PROGRESS IN EPISODIC MEMORY RESEARCH

EDITED BY: Ekrem Dere, Armin Zlomuzica, Angelica Staniloiu and Hans J. Markowitsch

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PROGRESS IN EPISODIC MEMORY RESEARCH

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Episodic memory refers to the ability to remember personal experiences in terms of what happened and where and when it happened. Humans are also able to remember the specific perceptions, emotions and thoughts they had during a particular experience. This highly sophisticated and unique memory system is extremely sensitive to cerebral aging, neurodegenerative and neuropsychiatric diseases. The field of episodic memory research is a continuously expanding and fascinating area that unites a broad spectrum of scientists who represent a variety of research disciplines including neurobiology, medicine, psychology and philosophy. Nevertheless, important questions still remain to be addressed. This research topic on the Progress in Episodic Memory Research covers past and current directions in research dedicated to the neurobiology, neuropathology, development, measurement and treatment of episodic memory.

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EDITORIAL
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Editorial: Progress in Episodic Memory Research

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Keywords: episodic memory, episodic-like memory, episodic future thinking, mental time travel, animal feed

The Editorial on the research topic

Editorial: Progress in Episodic Memory Research

Episodic memory refers to the ability to mentally time travel into the past and to remember personal experiences in terms of what happened and where and when it happened and to be autonoetically aware of it (Tulving, 2002). Humans (and perhaps also animals) are able to remember the specific perceptions, emotions and thoughts they had during a particular experience. This highly sophisticated and unique memory system is extremely sensitive to cerebral aging, neurodegenerative and neuropsychiatric diseases.

Episodic memory, as the sum of our experiences, is the supporting pillar of our identity and reminds us about our preferences and aversions, our strengths and weaknesses and helps us to anticipate how we will think, feel and behave in the future. Therefore, episodic memories are extremely useful for solving problems in the present and to plan for the future (Breeden et al., 2016).

The field of episodic memory research is a continuously expanding and fascinating area that unites a broad spectrum of scientists who represent a variety of research disciplines including neuroscience, behavioral genetics, medicine, neuropharmacology, psychology and philosophy. Nevertheless, important questions still remain to be addressed.

This research topic on the Progress in Episodic Memory Research covers past, current and future directions in research dedicated to the neurobiology, neuropathology, development, measurement and rehabilitation of episodic memory. A total of 171 high-rank international scientists have contributed to a compilation of 43 articles.

Among these 43 articles the reader will find (already well cited) original research (Alston et al.; Bai et al.; Barbosa et al.; Baumann et al.; Chen et al.; Coman et al.; Dalton et al.; Denkova et al.; Denkova et al.; Guillery-Girard et al.; Habermas and Diel; Henke et al.; Kanatsou et al.; Kinugawa et al.; Meyer et al.; Mulder et al.; Rauchs et al.; Reber et al.; Risius et al.; Shafer and Dolcos; Sperduti et al.; Staniloiu et al.; Todd et al.; Xiu et al.), opinion (Szpunar et al.) and review articles (Brod et al.; Friedman; Griffin and Hallock; Irish and Piguet; Mizumori; Muller; Murray and Kensinger; Pause et al.; Pergola and Suchan; Schnider; Souchay et al.; Werner et al.; Zlomuzica et al.), as well as hypothesis and theory papers (Dalla Barba and La Corte; Klein; Urbanowitsch et al.; Vandekerckhove et al.; Yassa and Reagh) from both human and animal research disciplines.

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With this *Frontiers eBook*, we (the editors) aimed to cover the full diversity of methods and theoretical approaches to unravel this veritable "marvel of nature" (Tulving, 2002) that we call episodic memory.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

Breeden, P., Dere, D., Zlomuzica, A., and Dere, E. (2016). The mental time travel continuum: on the architecture, capacity, versatility and extension of the mental bridge into the past and future. *Rev. Neurosci.* doi: 10.1515/revneuro-2015-0053. [Epub ahead of print].

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi: 10.1146/annurev.psych.53.100901.135114

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REVIEW ARTICLE
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Perspectives on episodic-like and episodic memory

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Episodic memory refers to the conscious recollection of a personal experience that contains information on what has happened and also where and when it happened. Recollection from episodic memory also implies a kind of first-person subjectivity that has been termed autonoetic consciousness. Episodic memory is extremely sensitive to cerebral aging and neurodegenerative diseases. In Alzheimer's disease deficits in episodic memory function are among the first cognitive symptoms observed. Furthermore, impaired episodic memory function is also observed in a variety of other neuropsychiatric diseases including dissociative disorders, schizophrenia, and Parkinson disease. Unfortunately, it is quite difficult to induce and measure episodic memories in the laboratory and it is even more difficult to measure it in clinical populations. Presently, the tests used to assess episodic memory function do not comply with even down-sized definitions of episodic-like memory as a memory for what happened, where, and when. They also require sophisticated verbal competences and are difficult to apply to patient populations. In this review, we will summarize the progress made in defining behavioral criteria of episodic-like memory in animals (and humans) as well as the perspectives in developing novel tests of human episodic memory which can also account for phenomenological aspects of episodic memory such as autonoetic awareness. We will also define basic behavioral, procedural, and phenomenological criteria which might be helpful for the development of a valid and reliable clinical test of human episodic memory.

Keywords: Alzheimer disease, dissociative disorders, emotional memory, episodic memory, mild cognitive impairment, spatial memory, temporal order memory, test development

INTRODUCTION

Learning and memory are indispensable capacities for humans and animals, since they permit adaptive behavior and promote the survival of the individual and the species. For example, they allow animals to revisit places where food or mating resources can be found and to avoid places where odor trails of predators were present. In general, they allow flexible and adaptive behavior in response to slow or sudden changes in the environment. The importance of learning and memory for the everyday life in humans becomes evident when one considers the decomposed personality structure in people who have lost access to information about emotionally relevant life events, such as in the case of demented patients.

Clinical studies with brain-injured patients and lesion studies in animals have revealed multiple memory systems in the brain with distinct neuroanatomical substrates and which are specialized for the learning of specific material such as how to play piano or the contents of a textbook (Squire, 2004). Accordingly, long-term memories can be divided into declarative and non-declarative memories. Declarative or explicit memories are conscious, can be voluntarily accessed and can be verbalized. In contrast non-declarative memories are not conscious and the contents of these memories cannot be verbalized. Declarative memories can be further subdivided into semantic and episodic memories. Semantic memories refer to facts and rules and basic knowledge about the world (Squire, 2004). In contrast, episodic memories refer to single events or personal experiences that also contain information about the spatial and temporal context of these events. Episodic memories also contain a blueprint of the internal state of the individual during encoding, e.g., its emotions, perceptions, and thoughts (Dere et al., 2008, 2010).

Due to its complexity of being a multi-dimensional memory trace that is distributed across the central nervous system and since it is established on a single occasion, episodic memory is highly vulnerable to disease conditions and easily disturbed (Aggleton and Brown, 1999; Aggleton and Pearce, 2001). Impairments in episodic memory function are observed in individuals with Mild Cognitive Impairment (MCI), in neurodegenerative diseases such as Alzheimer's Disease (AD), Huntington's Disease (HD), and Parkinson's Disease (PD) and also in a number of psychiatric diseases including Schizophrenia, Major Depression (MD), and dissociative disorders.

In this review we will describe the concept of episodic memory, and present human disease conditions that are associated with

episodic memory impairment. In the main part of this review, we will describe currently used tests of episodic memory function and discuss their validity. Hereby, we will discuss the implications of animal research on episodic-like memory for the theory and measurement of episodic memory. We will also describe a new concept of episodic memory that addresses the important questions of what is actually triggering episodic memory formation and its retrieval, and why some events are stored only transiently and others permanently. Finally, we will define basic criteria for the development of valid tests of episodic-like memory.

ENDEL TULVING'S CONCEPT OF EPISODIC MEMORY

The concept of episodic memory was developed by Endel Tulving in the early 70s (Tulving, 1972, 1983). At this time Tulving defined episodic memory rather technically as a memory system specialized to store specific idiosyncratic experiences in terms of what happened and where and when it happened. This initial definition is amenable to operationalization using a pure behaviorist approach to measure learning and memory performance (Dere et al., 2008, 2010) and has stimulated the development of what, where, and when paradigms for testing whether animals have the capacity to form episodic memories (Clayton and Dickinson, 1998; Dere et al., 2005a; Roberts et al., 2008).

In later work, Tulving widened the concept of episodic memory to include prerequisites of a fully developed episodic memory system (Tulving, 2001, 2002). Additionally, he described phenomenological processes that are specifically associated with the retrieval of episodic but not semantic memories. According to Tulving, episodic memory depends on a *self* (the awareness of the own existence) that goes along with *autonoetic awareness* (the awareness that remembered personal experiences have happened to oneself, are not happening now, and are part of one's personal history). Furthermore, Tulving proposed that humans have a *sense of subjective time* which enables them to distinguish between mental representations of the *self* in the past, present, and future (Tulving, 2001, 2002). Recently, the definition of episodic memory has been expanded by Klein (2013; this issue) by postulating that the core features of episodic memory in terms of a memory for what, happened, where and when are also shared by semantic memory and that episodic recollection requires the coordinated function of a number of distinct, but interacting, "enabling" systems. As enabling systems Klein postulates the para-mnestic constructs "ownership," "self," "subjective temporality," and "agency" that are necessary for episodic or autonoetic recollection in the sense of Tulving (2001, 2002).

It is further assumed that the type of subjective awareness provided by episodic or autonoetic recollection is relational rather than intrinsic in nature. Klein also assumes that the latter would imply that in some patient populations autonoetic recollection can be disturbed while core elements of episodic-like memory remain intact and are indistinguishable from the content of semantic long-term memory (Klein, 2013).

Nevertheless, it is obvious that the assessment of these phenomenological aspects during the retrieval of episodic memories is difficult to obtain by objective methods (Pennartz, 2009; Tagini and Raffone, 2010; Aleksander and Gamez, 2011). The possibilities to develop tests of autonoetic awareness and episodic recollection will be discussed later in this article. In the second part of this review we will outline the advantages of a behavioral definition of episodic-like memory for the development of a test that can be used for diagnostic purposes in healthy and patient populations and that allows to measure whether at least episodic-like memory is intact. We will also discuss the possibilities to combine a test of episodic-like memory with a second test that measures phenomenological aspects of episodic memory including autonoetic awareness to capture all elements of human episodic memory.

IMPAIRMENTS OF HUMAN EPISODIC MEMORY

Episodic memory deficits are observed after medial temporal lobe injury (Nyberg et al., 1996) which includes important memory structures such as the hippocampus (Burgess et al., 2002) and amygdala (Markowitsch and Staniloiu, 2011), but also after lesions to the frontal cortex (Kirchhoff et al., 2000) and diencephalic structures, such as the mediodorsal thalamus and the mammillary bodies (Tsivilis et al., 2008; Wolff et al., 2008).

Episodic memory impairments have also been demonstrated in the course of healthy aging (Tulving, 1983; Shing et al., 2010), the acute phase following mild traumatic brain injury (Dickerson and Eichenbaum, 2010; Tsirka et al., 2010), and in a variety of neuropsychiatric diseases (Butters et al., 1987; Dere et al., 2010). Furthermore, it seems that episodic memory deficits usually precede more global cognitive impairments associated with neurodegenerative diseases such as AD or PD (Williams-Gray et al., 2006; Dubois et al., 2007). Therefore, one can view episodic memory functioning as a highly sensitive indicator or seismograph of incipient brain pathology which manifests well before the full dimension of the disease becomes evident at the psychological and behavioral level.

MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Presently, more than 24 million individuals across the world suffer from dementia and the majority of these cases is likely to be caused by AD. This high prevalence is predicted to double every 20 years because of the unprecedented level of aging in developed countries and the increased life-expectancy in the fast developing threshold countries (Ballard et al., 2011). The major histopathological hallmarks of AD include the loss of synapses, neurodegeneration, extracellular amyloid plaque deposits, and intracellular neurofibrillary tangles (Yankner, 1996a,b; Ballard et al., 2011), affecting brain areas within the medial temporal lobe, such as the entorhinal cortex and the hippocampus (Schwindt and Black, 2009). AD is a progressive, irreversible, and severely disabling disorder of memory and cognition that inevitably results in the need of intensive care and death. Accordingly, the health-care costs associated with the disease are exceptional high. There is a preclinical period covering several years in both AD and other dementias, called MCI, during which early and mild cognitive deficits can be identified (Brand et al., 2003; Galluzzi and Frisoni, 2008; Bordet et al., 2010). On average 50% of the individuals with MCI will develop AD within a few years (Trojanowski et al., 2010). Cognitive decline in early stages of AD typically begins with deficits in episodic memory (Bäckman et al., 2004; Ringman, 2005; Sarazin and Dubois, 2005; Thomas-Anterion and Laurent, 2006; Bäckman and Small, 2007; Dubois et al., 2007; Small and Bäckman, 2007; Schwindt and Black, 2009).

Until to date, there is no definite diagnostic test available which could identify AD in living patients (Reitz et al., 2010). Furthermore, the establishment of diagnostic tools for AD is time-consuming and expensive. Imaging tests include the measurement of amyloid-beta burden with PET (Nordberg et al., 2010) or measurements of hippocampal and frontal cortex volume with MRI (Wagner, 2000). Other tests include the analysis of cerebrospinal fluid biomarkers, e.g., the concentration of Aβ-oligomerization, Aβ-fragments, or phosphorylated-Tau (Blennow, 2010a,b; van Rossum et al., 2010). Although, these measurements have a high predictive value for identifying individuals in the prodromal stage of AD among patients with MCI (Hampel et al., 2010), these tests are too time-consuming, invasive, and expensive for being adopted as a routine screening. Therefore, AD is often unrecognized or misdiagnosed in its early stages.

Currently, the patient populations used to test the efficiency of drugs to ameliorate AD symptoms or its pathology in clinical trials are either very heterogeneous, as in the case of individuals with MCI, or patients are in a progressed stadium of AD where the effect of the drug is limited by extensive neurodegeneration. In fact, the potential of pharmacotherapy to ameliorate symptoms and/or pathology in AD has not yet been fully explored because of the difficulty to identify patients in a prodromal stage of AD (Blennow, 2010a,b).

The cognitive tests currently used for the diagnosis of AD are unspecific and cannot exclude cognitive impairments induced by other diseases. Furthermore, these tests are not sensitive to very mild forms of cognitive impairment (Pike and Savage, 2008). Thus, the main problem is that by the time the patient is diagnosed with AD, the disease had been progressed to a stadium in which pharmacological, immuno- (Weiner and Frenkel, 2006), and gene-therapy treatments (Urbaniak-Hunter et al., 2010) have only limited effects because of the advanced neurodegeneration in the target structures such as the frontal cortex or the hippocampus.

Therefore, there is a need for the development of a new cognitive marker of the presymptomatic stage of AD based on a test of episodic memory functioning. With such a diagnostic episodic memory test at hand it might be possible to identify individuals with a presymptomatic stage of AD among individuals with MCI. It might then be possible to delay the onset of the disease or to decelerate its progression with the currently available anti-Alzheimer disease treatments (Di Stefano et al., 2011; Pettersson et al., 2011).

DISSOCIATIVE AMNESIA

Dissociative amnesia also known as functional or psychogenic amnesia is a disease condition characterized by a transient and selective inability to retrieve episodic and autobiographical memories after experiencing traumatic events that have been associated with intolerable high levels of enduring stress (Brandt and Van Gorp, 2006; Reinhold and Markowitsch, 2009). Patients with dissociative amnesia have generally no impairment in the formation and retrieval of new memories as in the case of organic anterograde amnesia. The transient episodic memory retrieval deficit can be confined to episodic memories of a certain age and usually includes the memory for the traumatic event. It is assumed that the inability to retrieve traumatic events serves as a protective mechanism that inhibits the conscious recollection of self-endangering memories (Kapur, 1991).

Imaging studies have revealed functional changes in the activity of the right temporal-frontal region and in the inferior-lateral prefrontal cortex in brains of patients with dissociative amnesia during the resting state (Brand et al., 2009). Furthermore, it has been proposed that the inability to retrieve episodic memories in patients with dissociative amnesia might be related to functional disturbances in the activity of the precuneus, the lateral parietal, the right dorsolateral, and polar prefrontal cortex (Markowitsch et al., 1997). There is also recent evidence suggesting that the inability to retrieve episodic memories in dissociative amnesia is correlated with functional alterations of left posterior parietal cortex (Arzy et al., 2011).

Dissociative amnesia is an example for the disruption of episodic memory function induced by extreme levels of emotional activation or stress that is enduring and uncontrollable. The case of dissociative amnesia suggests that extreme levels of emotional activation or stress do not interfere with the formation of durable episodic memories but rather with their accessibility during attempts of retrieval. With regard to the findings with dissociative amnesia, the relationship between emotional activation and the formation of durable episodic memories could be précised as follows: Too low levels of emotional activation are not suited to consolidate episodic memories into long-term memory, while extreme levels of emotional activation or stress (transiently) impair the retrieval of durable episodic memories. This hypothesis will be outlined in detail below.

ASSESSING EPISODIC MEMORY

CONVENTIONAL MEASURES

The pertinent literature indicates that even the measurement of human episodic-like memory (without an explicit test of episodic or autonoetic recollection) based on the rather narrow (initial) definition of Tulving (1972) as a memory system that receives and stores personal experiences in terms of what, where, and when information was and is a daunting task, with only very few successful approaches available (Dere et al., 2004, 2010). For example, due to the lack of a valid test, the utility of subtests of the Mini Mental Status Examination Test (Carcaillon et al., 2009) or the Wechsler Memory Scale (Humphreys et al., 2010) have been evaluated as tools to measure episodic memory or episodic-like memory. The subtests of the Wechsler Memory Scale only measures verbal and visual memory and not episodic memory or episodic-like memory as defined above. The Mini Mental Status Examination Test is used for assessing the severity of dementia, comprising items on semantic memory and executive functions. Thus, both tests are not suited to detect selective episodic memory or episodic-like memory impairments that are associated with, e.g., MCI.

Currently used more specific tests of episodic memory or episodic-like memory function either measure the learning and reproduction of study list items such as the California Verbal Learning Test (Woodard et al., 1999; Fine et al., 2008; Lekeu et al., 2010) or are based on verbal or written reports of autobiographical events, such as in the Autobiographical Interview (Gilboa et al., 2005; Dreyfus et al., 2010; Irish et al., 2011).

VERBAL LEARNING TESTS

In the recognition test studies, healthy participants or patients are requested to discriminate previously studied word or picture items from novel items (e.g., California Verbal Learning Test, Grober and Buschke, 1987). In some studies the maintenance of the learned material due to rehearsal in-between the encoding and retrieval sessions is prevented by an intervening and distracting task. The Rey Auditory Verbal Learning Task is based on the interference induced by the consecutive learning of two word lists and the immediate and delayed recall of the first list (Lezak, 1995).

The problem with verbal learning tests is that they do not explicitly measure whether the spatial and temporal context of the learning event is indeed recalled and often there is no spatial and temporal component implicated in the way the verbal memory is tested. Although, one can certainly assume that healthy adults are potentially able to remember where and when the recognized items have been presented, this is not sure in patient populations so that this ability has to be measured directly. Therefore, simple recognition tests cannot be used for episodic memory or episodic-like memory assessment in patient populations. Another problem associated with simple word list or picture recognition tests is that the participant or patient is instructed to memorize the learning material. This instruction is very likely to activate semantic instead of episodic memory systems for learning and consolidation of the learning material.

THE AUTOBIOGRAPHICAL INTERVIEW

Questionnaires for autobiographical or important life events have also been used to asses episodic memory function (Levine et al., 2002; Piolino et al., 2009; Dreyfus et al., 2010). Kopelman et al. (1989), have developed a semi-structured interview schedule, that assesses the recall of autobiographical incidents and of "personal semantic" memory across three broad time periods termed: "childhood," "early adult life," and "recent" events/information. With the term "personal semantic" memory, they refer to factual knowledge about a person's own past (e.g., addresses where lived, names of teachers/friend, colleagues at work, etc.). Thus, individuals are asked to recall a number of events from different periods of their life such as early childhood etc. or to recall a series of positive, negative, and neutral episodes from their lives. Usually, the participants or patients are asked to describe complete episodes that happened at a certain time and place. The verbal or written reports on events are then scored according to the frequency of episodic and non-episodic detail categories given. Episodic details refer to event, time, place, perceptual, thought, and emotion information (Kopelman et al., 1989). The general idea is that the fewer episodic details remembered for a given life event, the stronger the impairment in episodic memory functioning. However, there are a number of problems associated with this form of episodic memory assessment.

Generally, autobiographical memories are likely to be retrieved and narrated many times and due to their constructive and dynamic nature there might be changes in the contents and stability of a memory across time (e.g., due to reconsolidation and interference phenomena) (Schacter et al., 1998; Walker et al., 2003; Earles et al., 2008). Therefore, it is not always clear what type of memory (e.g., episodic or semantic memory) is actually measured by autobiographical memory tests. To account for this problem, tests have been designed that aim to distinguish between episodic and semantic components of autobiographical memory by scoring the spatio-temporal uniqueness of events (Levine et al., 2002; Piolino et al., 2009). Another problem is that episodic memory or episodic-like memory function is obviously judged by the assessment of the episodic memories that *can* be retrieved.

In early stages of neurodegenerative diseases such as MCI and AD autobiographical memories for personal life events which have been established decades before the onset of memory complaints are, although still accessible (Squire and Alvarez, 1995), possibly not completely normal. It has been shown that such autobiographical memories are overgeneralized, contain less specificity, and are less vivid (Murphy et al., 2008; Donix et al., 2010; Martinelli et al., 2013). Nevertheless, it is reasonable to assume that any impairment in episodic memory or episodic-like memory function should also impair the ability to encode and consolidate new or more recently formed episodic memories. These difficulties should manifest themselves as an inability to form novel episodic memories possibly independent of, or in addition to, changes in the ability retrieve episodic memories. Although the recollection of overgeneralized autobiographical memories for personal life events might be a hint for disturbed episodic memory function, reports on more recent events are probably more valid measures of the current status of episodic memory function.

Furthermore, the performance is also dependent on factors such as verbal competence, the ability and disposition to express feelings and emotions, the level of education, and pre-morbid verbal intelligence.

In conclusion, there is still a need for a valid standardized test to induce episodic-like memories and measure their retrieval. The arguments raised above suggest that it might be better to measure novel episodic memories rather than just ask the participant to elaborate on memories from the individual's personal history, without having the option to control the exact circumstances and the time of episodic memory formation.

ANIMAL RESEARCH ON EPISODIC-LIKE MEMORY

Animal research with rats and mice allows the study of the neurobiological mechanisms that might underlie episodic-like memory formation and retrieval with methods that are not available in human research. The animal research on episodic-like memory has its origins in now classic experiments on food-hoarding behavior in birds performed by Nicola Clayton and Anthony Dickinson (Salwiczek et al., 2009, for review). This line of research will be briefly discussed in the following paragraph. Thereafter we will discuss the importance of using one-trial memory paradigms (contextual fear conditioning and novelty-preference) which bear the unique capacity of being translatable to human episodic-like memory research.

FOOD-HOARDING PARADIGMS

The first evidence for episodic-like memory in animals was provided by Clayton and Dickinson (1998) showing that birds (scrub jays) are able to remember where and when they have cached a particular food item. In the studies that followed, it was reported that corvids are also able to use tools (Cheke et al., 2011), show object

permanence (Salwiczek et al., 2009), plan for the future (Raby et al., 2007), and might have a theory of mind (Emery and Clayton, 2004; Dally et al., 2006; Grodzinski and Clayton, 2010; but see Roberts, 2002; Dere et al., 2008; Rattenborg and Martinez-Gonzalez, 2011 for critical discussion).

In fact, all these remarkable abilities of corvids have been demonstrated with behavioral paradigms that are in one or the other way related to food caching and retrieval behavior which is very likely to be a genetically fixed instinctive behavior. In other words, all of these abilities might be restricted to a narrow class of content or what information. In contrast, the human episodic memory is not restricted to a specific type of events or stimuli. Therefore, it is indispensable to show that these birds are also able to perform all of these sophisticated tasks with stimuli other than food, such as the objects which do not have a biologically significant meaning to the animals (despite being of course novel stimuli) used in the episodic-like memory task developed by Dere et al. (2005a).

CONTEXTUAL FEAR CONDITIONING

In the one-trial contextual fear paradigm, the animal receives a food shock upon the transition from a brightly lit large chamber into a smaller dark one (Sara et al., 1975; Ebenezer, 1988; Rudy and Sutherland, 1995; Rudy et al., 2004). If the animal is reintroduced to the big chamber, e.g., after a delay of 24 h, one finds that the animal avoids the normally preferred dark chamber. Thus, one-trial contextual fear conditioning can be described as a type of associative learning that is associated with a strong emotional arousal due to the sudden application of a painful stimulus in a specific spatial context. The formation of this memory seems to depend on hippocampal NMDA-receptors in the CA3 region (Cravens et al., 2006). It can be acquired in one trial, leads to a memory that is quite long-lasting (up to months), and is sensitive to hippocampal lesions (Anagnostaras et al., 2001; Lehmann et al., 2007). Therefore, there are some similarities between one-trial contextual fear conditioning and human episodic-like memory.

However, concerning the formation of episodic memory, the main problem that is associated with the contextual fear paradigm is that it does not measure whether the animals remember the temporal context of the aversive event (when information). Furthermore, human episodic memories are not restricted to fearful events, but also cover pleasant events (Ehrlichman and Halpern, 1988; Hamann et al., 1999). Nevertheless, the contextual fear conditioning paradigm has been useful to study the neurobiological mechanisms that might underlie one-trial spatial memory formation in rodents (Tronche et al., 2010; Li et al., 2011).

THE NOVELTY-PREFERENCE PARADIGM

The novelty-preference paradigm is based on the attraction of rats and mice by novel objects (Dere et al., 2007; Ennaceur, 2010; for a review see Dere et al., 2007). If rodents have the choice between an old and novel object they spent more time exploring the more interesting novel object suggesting that they remember the physical characteristics of the old object. The exploration of a novel object reflects approach behavior and likely to be motivated by an emotional activation that is rather pleasant to the animal and triggers episodic-like memory formation (reviewed in Dere et al., 2010). However, rodents prefer old objects when they have been placed in novel locations which render these objects more interesting as compared to old objects that are placed in a familiar location, which is taken as evidence for spatial object memory (Assini et al., 2009). In addition, rodents prefer objects which they have not seen very recently over those they have investigated more recently, which is taken as a measure for temporal order memory (Mitchell and Laiacona, 1998). By combining these different versions of the novelty-preference paradigm Dere et al. (2005a,b) tested whether rodents are able to remember specific events in terms of what happened where and when.

THE EPISODIC-LIKE MEMORY TEST

The episodic-like memory test for rats and mice (Dere et al., 2005a; Kart-Teke et al., 2006) allows the simultaneous measurement of the memory for the temporal order of objects presented within an open-field as well as the spatial positions in which these objects have been encountered. The test is also able to detect whether what, where, and when information has been integrated into a unified multi-dimensional episodic memory (Kart-Teke et al., 2006; Zlomuzica et al., 2007). In brief, each animal receives two sample trials with four identical copies of a novel object and an inter-trial interval of 50 min followed by a test trial in which two objects from the first sample trial (old objects) are presented together with two objects known from the second sample trial (recent objects). During the test trial one of the old and one of the recent objects are displaced to a novel location. It has been demonstrated that rats and mice are able to associate object-, spatial-, and temporal information after a single exposure to such stimulus constellations (Dere et al., 2005a,b, 2007). This remarkable ability is in accord with the concept of episodic-like memory and can be further classified as a kind of one-trial contextual learning (Kart-Teke et al., 2006; Zlomuzica et al., 2008).

BEHAVIORAL CRITERIA FOR THE MEASUREMENT OF EPISODIC-LIKE MEMORY

Findings from animal research were useful for the better understanding and definition of the conditions that might lead to episodic-like memory formation and its retrieval as well as for the generation of objective behavioral criteria by which the different features of episodic-like memory can be operationalized experimentally and can be assessed in both animals and humans (Clayton and Dickinson, 1998; Dere et al., 2005a,b, 2006). Accordingly, it has been proposed that episodic-like memory and episodic memory formation is an automatic, one-trial learning process based on the principles of one-trial contextual conditioning that is induced by a strong pleasant or aversive emotional activation (Dere et al., 2010). The generation of an episodic-like memory itself can be inferred from behavioral expressions referring to the content (what happened), place (where did it happen), and temporal context (in terms of the sequence of events attended) of personally experienced emotional events (Dere et al., 2006, 2008, 2010). Based on this behavioral definition of episodic-like memory a novel paradigm to induce and measure this type of memory non-verbally via quantifiable and reproducible motor responses in humans has been devised that will be presented below (Pause et al., 2010).

EMOTIONS TRIGGER EPISODIC MEMORY FORMATION

In order to measure novel episodic or episodic-like memories in the laboratory for research and diagnostic purposes it is necessary to define the properties of the events which induce episodic memory formation. Usually, only a subset of events that have occurred in the course of a day can be recalled after a few hours and the percentage of events that can be recalled decreases further if the delay between encoding and recall is extended to days, weeks, months, and years. The important question here is why are some events only stored for a few hours in the episodic memory system while others are stored permanently.

According to a distinction in memory duration, the classic test of episodic memory "please describe your breakfast this morning" would be a test of short-durable episodic memory, because it is obvious that the question "please describe your breakfast on Monday the week before last" will not yield a vivid description of this event. In contrast, the event of a car accident that occurred later on that particular Monday morning when the person was for example driving to its work place will be permanently remembered in great detail. It has been proposed that the impact of the trigger for episodic memory formation that decides for how long an event is stored in episodic memory is dependent on the emotional arousal that is associated with that event (Libkuman et al., 2004; Dere et al., 2010). Here, the rule might be that the stronger the emotional activation, the longer the durability of the episodic memory. Of course, this does not affect the fact that the durability and content of memories can also be modulated by factors such as rehearsal or the number of previous recalls of the memory (Zimmer et al., 2003; McKenzie and Eichenbaum, 2011). Furthermore, it is important to note that extreme emotional activation (e.g., stress) can disrupt episodic memory function similar to other types of memory. An example for such stress-induced impairment of episodic memory function is discussed under the section dealing with dissociative amnesia.

Furthermore, it is possible that the relationship between episodic memory performance and the degree of emotional activation during the encoding of episodic information has the form of an inverted U-shaped curve as it has been described for the dose-response function between orally administered cortisol and explicit memory performance in humans (Abercrombie et al., 2003; Baldi and Bucherelli, 2005). This assumption implicates that excessive emotional activation similar to insufficient emotional activation would impair episodic memory formation. One example for impaired episodic memory formation after excessive emotional activation is that of a trauma memory which can be either fragmentarily or incorrectly remembered (Bower and Sivers, 1998; van der Hart and Nijenhuis, 2001; Brewin, 2011). Moreover, emotional arousal might not be only a trigger for episodic memory formation but might also play a role in binding of different features of an event into a unified episodic memory (Nashiro and Mather, 2011).

One prediction of the necessity of emotional arousal for the establishment of long-durable episodic memories would be that bilateral amygdala damage impairs episodic memory function. In this regard, it has been proposed that the amygdala contributes to the integration of emotion, perception, and the memory for past autobiographical events, plays an integral part in the establishment and maintenance of an integrated self, and provides retrieval cues during the memory search for emotionally significant events (Markowitsch and Staniloiu, 2011). Evidence for an implication of the amygdala for the encoding and retrieval of episodic memories has been provided by the examination of patients with Urbach–Wiethe syndrome who suffer from relatively selective bilateral lesions of the amygdala (Hurlemann et al., 2007). In fact, it has been reported that Urbach–Wiethe patients show an impairment of the memory for autobiographic episodes but not for autobiographic facts (Wiest et al., 2006). Furthermore, it has been reported that a 54-year-old woman with bilateral damage to the amygdala showed impaired episodic memory performance for stimuli that elicited an arousal response (taboo words) but not for emotional stimuli which did not elicit an arousal response (Phelps et al., 1998).

THE TEMPORAL COMPONENT OF EPISODIC MEMORY

A main difference between episodic and semantic memory is that the episodic memories have also a temporal connotation are time-dated or endowed with time-tags such as that something has happened "this morning" or "last summer" (Tulving, 2001, but see also Klein, 2013 this issue for a different view). However, in humans the perception of time and the assessment of the duration of events are not represented on a linear time scale (Pöppel, 1997; Roberts, 2002). In this regard, Friedman (1996) speaks of a "chronological illusion," and proposes that the memory for time is rather reconstructive and inferential in nature.

We have proposed that temporal information is either stored as succession or order information relative to other events already stored in episodic memory or is reconstructed during the recall processes using anchor events (events for which an episodic memory exists) (Dere et al., 2006). It is reasonable to assume that the temporal context of a particular event is either encoded in relation to, or inferred from its occurrence before or after, other "anchor events." One of which is proximal in terms of just preceding or following the event to be temporally specified, whereas the other is more distal that is the anchor event stands at the beginning or end of a larger sequence of events centered by the event to be temporally specified. The when component of an episodic memory can thus be operationalized by successively presenting two or more distinct events and by probing whether the participants are able to remember their order of occurrence (Dere et al., 2006, 2008).

THE RETRIEVAL OF EPISODIC MEMORY

One difficulty that is associated with the traditional concept of episodic memory is that they do not specify the circumstances that lead to the retrieval of episodic memories besides postulating that it should be a "free recall" instead of a "cued" recall (Yonelinas, 2002). This assumption might not be correct since it is unlikely that any memory retrieval either episodic or semantic occurs without a cue stimulus which triggers memory retrieval (Dere et al., 2004; McCabe et al., 2011; Unsworth et al., 2011). There must be a cue stimulus present either produced internally (e.g., a thought) or externally, within the environment that triggers the memory retrieval (Light and Albertson, 1989). Otherwise our episodic and semantic memories would be retrieved in an uncontrolled and highly disturbing manner.

Recently, it could be demonstrated that odors are highly valid stimuli cuing episodic or autobiographic memory contents (Aggleton and Waskett, 1999; Saive et al., 2013). Odor evoked memories are experienced as more emotional and are associated with feelings of being brought back in time to the occurrence of the event (Masaoka et al., 2012; Arshamian et al., 2013). The potency of odors to evoke highly vivid episodic memories has been discussed to be due to the emotional nature of olfactory stimuli (Pause et al., 2008; see Laudien et al., 2008; Adolph and Pause, 2012).

The new concept of episodic memory presented here holds that episodic memory formation is based on principles similar to one-trial contextual conditioning and that its retrieval depends on the presence of a cue or conditioned stimulus. This concept is at variance with the traditional distinction between declarative and non-declarative memory (Squire, 2004) in which episodic memory is generally attributed to declarative memory, while classical conditioning, including contextual conditioning, is attributed to non-declarative memory. It seems that it is time to revise this useful nomenclature of long-term memory systems to better reflect the novel insights gained into the nature of episodic memory.

PROMISING NOVEL PARADIGMS

SPATIAL AND TEMPORAL ORDER MEMORY FOR EMOTIONAL PICTURES

In a reverse translational approach by Pause et al. the rationale and principles of the episodic-like memory test for rodents (Dere et al., 2005a,b; Kart-Teke et al., 2006) have been adapted to humans. Pause et al. (2010) developed a paradigm which measures the spatio-temporal memory for emotional and neutral pictures presented on an eight-quadrant computer-screen task. Visual stimuli were hidden in four out of eight quadrants on a computer-screen. Each of these quadrants could be highlighted by pushing a corresponding button on a keyboard which either revealed a visual stimulus for 100 ms or remained black. Participants had to remember on which occasion (when) and at which position (where) a specific picture (what) has been encountered. It was investigated whether exploratory button presses can be used as a non-verbal behavioral expression of what, where, and when memory. Verbal what, where, and when memory performance was measured by a standardized interview.

Pause et al. (2010) also examined whether the variation of the visual stimuli in terms of concreteness and emotional content would have an effect on what, where, and when memory performance or quadrants exploration. In the verbal test, healthy adult participants were able to recollect the details and the spatio-temporal context of visual stimuli with combinations of high or low concreteness and neutral or emotional content after retention delays up to 72 h. The number of button presses to each of the four quadrants containing visual stimuli was positively correlated with verbal what, where, and when memory performance.

These results demonstrate that what, where, and when memory can be induced experimentally and can be measured by motor behavior which can serve as a non-verbal correlate of episodic memory performance (Pause et al., 2010). Compared to classical methods this novel paradigm is certainly an improvement as it measures novel long-term memories for what, where, and when information. However, since the participants were instructed to memorize the learning material, the task might not only have involved episodic memory mechanisms. Therefore, a slightly different version of this paradigm has been applied in young and elderly participants (Kinugawa et al., 2013, this issue). Here, the participants were not informed to memorize the test items and the memory retrieval was not foreseeable for the participants. Furthermore, explicit memory performance was tested already 2.5 h after the initial learning phase. It was found that the young group (age: 21–45) had significantly higher episodic memory scores as compared to both the middle (age: 48–62) and aged group (age: 71–83). The latter two groups performed not significantly different from each other. The results suggest that this novel test of what, where, and when memory that measures the core components of an memory for event, spatial, and temporal information and in addition is likely to probe the ability to form new episodic memories is suited to detect age-related impairments in what, where, and when memory performance. Due to its simplicity, its one-trial nature and the option of a non-verbal measurement this task could be probably adapted to clinical populations.

THE KENSINGER EPISODIC-LIKE MEMORY TASK

In a recent fMRI study by Kensinger et al. (2011) on the role of the amygdala for the encoding of episodic-like memories the participants studied four sets of emotional pictures. It was found that amygdala activity was correlated with item-specific details of the learning material used and the subjective assessment of memory vividness, but not with the diversity of episodic details remembered (Kensinger et al., 2011). In this study, each picture was presented in one out of four quadrants of a monitor screen. On the retention test performed 30 min after the presentation of a total of four picture sets, verbal labels corresponding to the pictures viewed were presented. This approach aims to induce and measure a memory for what, where, and when. The what and where components have been operationalized by different pictures presented in different quadrants on a monitor screen. The temporal component of episodic-like memory was operationalized by the four different sets of pictures. In general the task was associated with a rather high memory load. The participants had to memorize four sets with a total of 30 pictures and as well as their positions on the screen. Furthermore, the task performance certainly depended on pre-morbid learning abilities and the susceptibility to interference. For these reasons the task might be too complicated to be performed with individuals suffering, e.g., from MCI. Furthermore, a retention delay of only 30 min might not fall into the range of long-term episodic memory and retention performance might involve short-term memory phenomena such as recency effects. The combination of emotional pictures with spatial and temporal information is certainly a useful approach to identify the neuroanatomical substrates of episodic-like memory in humans.

VIRTUAL REALITY-BASED TASKS

Another reverse translational approach aims to induce and measure core elements of episodic-like memory such as spatial and temporal order memory in humans with a navigational "starmaze" task, initially developed to measure egocentric and allocentric spatial orientation in rodents (Rondi-Reig et al., 2006; Fouquet et al., 2011). Here the individual's ability to remember a sequential order

of choices during spatial navigation in a virtual reality environment is measured (Fouquet et al., 2010). The participant has to learn to reach a goal using the most direct path. During the multiple acquisition trials, the individuals can use allocentric (spatial reference memory) or egocentric (temporal order based) strategies to solve the task. Fouquet et al. (2010) propose that the use of the egocentric strategy to perform this task involves an "active, flexible, and complex integration of past and current states" which is a feature shared by episodic memory. Following this rationale it can be predicted that an individual with impaired episodic memory function would be forced to choose the allocentric strategy to learn the path through the virtual environment.

Allocentric orientation in a novel environment is a function which is critically dependent on the integrity of the hippocampal formation in rodents and humans. Furthermore, the hippocampus is also indispensable for the integration of spatial and temporal information into a unified episodic memory (Ranganath, 2010). In fact, animal studies have shown that rodents with hippocampal lesions shift to egocentric striatum-based strategies to solve spatial tasks and that healthy controls spontaneously use allocentric strategies and only shift to egocentric strategies if the former is not successful (Oliveira et al., 1997; DeCoteau and Kesner, 2000; Dere et al., 2001). Nevertheless, this approach is interesting and certainly worth of being evaluated with patient populations.

Yet another approach to measure episodic memory function using virtual reality technology has been recently communicated by Plancher et al. (2012a). In this study the authors argue that virtual reality-based tests allow to investigate episodic memory profiles in an ecological fashion, including the assessment of the memory for central and perceptual details, spatio-temporal contextual elements, and binding of these multi-dimensional information. The authors tested older individuals, patients with MCI as well as patients with early stages of AD. These groups were tested under active and passive exploration conditions and were instructed to memorize as many information as possible as well as all spatio-temporal information that was associated with detail information. As expected the performance of patients with AD was inferior to that of the patients with MCI and healthy older individuals. The authors found that spatial allocentric memory assessments discriminated between patients with MCI from controls and that active exploration was associated with better performance in all of the three groups.

Additional studies by this and other groups have further substantiated the important influence of enactment, exercise, and active engagement of subjects in the encoding phase (Madan and Singhal, 2012; Plancher et al., 2012b). The theoretical background of this line of research is derived from the concept of embodied cognition that holds that physical properties of the human body, particularly the perceptual and motor systems, modulate learning and memory formation (Madan and Singhal, 2012).

In conclusion virtual reality and enactment-based tests of episodic-like memory might allow measuring this function in a more ecological fashion. However, it is also important to avoid explicit instructions asking the participants to memorize the information presented, including precise instructions on what kind of information should be memorized. This kind of instruction might prompt the participants to use semantic learning strategies rather than incidental episodic memory encoding. It is important to note that although the recollection of episodic memories is associated with autonoetic awareness, its encoding is rather automatic and effortless (Zentall et al., 2008; Dere et al., 2010). Generally, any assessment of episodic-like and episodic memory should be unexpected.

BASIC CRITERIA FOR EPISODIC-LIKE MEMORY TEST DEVELOPMENT

Although, the above reviewed novel approaches to measure episodic-like memory have moved the field forward toward a valid and reliable test of episodic memory (besides of not probing autonoetic recollection) all of them have their pitfalls and are not easily applicable to patient populations. Similarly, animal research has led to the definition of behavioral criteria that are considered important for the measurement of episodic-like memory in animals and also for the measurement of episodic-like memory in humans (Griffiths and Clayton, 2001; Dere et al., 2008).

In the following we will outline seven basic criteria which should be met by a test of episodic-like memory. These seven criteria might facilitate the development of routine diagnostic tests of episodic-like memory for patient populations and tests to be utilized for the investigation of the neurobiological and electrophysiological substrates of episodic memory in healthy individuals.

First criterion, in order to be able to control the correctness of the episodic-like memory retrieved and also to control the time of encoding of these events, as well as to have the option to manipulate experimental variables that would affect episodic memory formation in healthy and patient populations differently, it is necessary to induce the episodic memories in the laboratory.

Second criterion, the participants of an experimental investigation or patients to be tested for episodic-like memory integrity should not receive any explicit instruction to memorize the episodic information. Otherwise, the episodic information might be acquired and retained by semantic memory systems, e.g., by rehearsing the episodic information until it is consolidated using a semantic memory system.

Third criterion, since long-durable episodic-like memory which are permanently stored are generally related to important life events which have been accompanied and probably induced by a relatively strong (but not excess, see above) emotional activation, the episodic information to be retained needs to have an emotional valence and should be associated with emotional arousal to be demonstrated at the level of physiological stress responses or autonomic activation associated with pleasant events.

Fourth criterion, the induction of the episodic-like memory must be per definition a one-trial learning event. The acquisition of episodic information presented repeatedly is always mediated through a semantic memory system.

Fifth criterion, the episodic information to be induced, retained and retrieved must include what, where, and when information. Episodic-like memory assessment has to include the measurement of the ability to remember what, where, and when information.

Sixth criterion, the memory test has to be unexpected and only the first recall is a valid measure of episodic-like memory performance. Generally, the possibility to perform re-tests or multiple assessments of the same individual with the same episodic memory test is therefore very limited.

Seventh criterion, the storage of long-durable episodic-like memories requires memory consolidation which requires the activation of specific genes and *de novo* synthesis of proteins (Abel and Lattal, 2001; Igaz et al., 2002). Drugs that block protein synthesis such as antibiotics have amnesic effects when administered immediately after the acquisition of new information (Schafe et al., 1999; Díaz-Trujillo et al., 2009) but not after delays of 60 min or more (Fulton et al., 2005; Rossato et al., 2007; Lima et al., 2009). Therefore, the memory test has to be performed after a retention interval of at least 60 min after presentation of the episodic information to be considered a fully consolidated long-term memory. Tests which adhere to these requirements can be considered as measuring episodic-like memory in a valid and reliable way.

BASIC CRITERIA FOR A TEST OF EPISODIC MEMORY

A valid test of human episodic memory should include the seven criteria defined above to qualify as a test of episodic-like memory and should also measure phenomenological aspects of episodic memory such as autonoetic awareness, self, subjective sense of time. This could be potentially done with a separate tests performed after the episodic-like memory test. In the past it has been attempted to measure autonoetic awareness with the remember/know procedure derived from the dual-process signal-detection theory (Yonelinas, 2002). With this method individuals are asked to learn a list of items and thereafter presented with items form the list and novel items. If the subject recognizes an item the participant is asked to state whether it "remembers" that the item was on the list or whether he/or she just "knows" that the item was on the list because of a feeling of familiarity. It is obvious that this procedure is not suited to capture the richness and complexity of Tulving's understanding of episodic memory (Tulving, 2002) "*Episodic memory is a recently evolved, late-developing, and early-deteriorating past-oriented memory system, more vulnerable than other memory systems to neuronal dysfunction, and probably unique to humans. It makes possible mental time travel through subjective time, from the present to the past, thus allowing one to re-experience, through autonoetic awareness, one's own previous experiences. Its operations require, but go beyond, the semantic memory system. Retrieving information from episodic memory (remembering or conscious recollection) is contingent on the establishment of a special mental set, dubbed episodic "retrieval mode." Episodic memory is subserved by a widely distributed network of cortical and subcortical brain regions that overlaps with but also extends beyond the networks subserving other memory systems. The essence of episodic memory lies in the conjunction of three concepts – self, autonoetic awareness, and subjectively sensed time.*"

CONCLUSION

Although, one can note some progress toward the goal of a valid and reliable test of episodic-like memory that can be utilized in clinical settings for diagnostic purposes the currently available approaches still have to be optimized and modified before they can be possibly adapted for patient populations. A valid test of episodic memory that also includes the phenomenological aspects of episodic memory is still lacking. The above criteria should help to approach the optimal solution more directly. It is hoped that this review will sensitize clinicians and researchers in the field of episodic memory to critically re-evaluate their current methods and tools to measure episodic-like or episodic memory and will induce a lively discussion concerning the urgent need to develop novel and better paradigms to measure episodic memory.

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REFERENCES

Abel, T., and Lattal, K. M. (2001). Molecular mechanisms of memory acquisition, consolidation and retrieval. *Curr. Opin. Neurobiol.* 11, 180–187.

Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., and Davidson, R. J. (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behav. Neurosci.* 117, 505–516.

Adolph, D., and Pause, B. M. (2012). Different time course of emotion regulation towards odors and pictures: are odors more potent than pictures? *Biol. Psychol.* 91, 65–73.

Aggleton, J. P., and Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav. Brain Sci.* 22, 425–444.

Aggleton, J. P., and Pearce, J. M. (2001). Neural systems underlying episodic memory: insights from animal research. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1467–1482.

Aggleton, J. P., and Waskett, L. (1999). The ability of odours to serve as state-dependent cues for real-world memories: can Viking smells aid the recall of Viking experiences? *Br. J. Psychol.* 90, 1–7.

Aleksander, I., and Gamez, D. (2011). Informational theories of consciousness: a review and extension. *Adv. Exp. Med. Biol.* 718, 139–147.

Anagnostaras, S. G., Gale, G. D., and Fanselow, M. S. (2001). Hippocampus and contextual fear conditioning: recent controversies and advances. *Hippocampus* 11, 8–17.

Arshamian, A., Iannilli, E., Gerber, J. C., Willander, J., Persson, J., Seo, H. S., et al. (2013). The functional neuroanatomy of odor evoked autobiographical memories cued by odors and words. *Neuropsychologia* 51, 123–131.

Arzy, S., Collette, S., Wissmeyer, M., Lazeyras, F., Kaplan, P. W., and Blanke, O. (2011). Psychogenic amnesia and self-identity: a multimodal functional investigation. *Eur. J. Neurol.* 18, 1422–1425.

Assini, F. L., Duzzioni, M., and Takahashi, R. N. (2009). Object location memory in mice: pharmacological validation and further evidence of hippocampal CA1 participation. *Behav. Brain Res.* 204, 206–211.

Bäckman, L., Jones, S., Berger, A. K., Laukka, E. J., and Small, B. J. (2004). Multiple cognitive deficits during the transition to Alzheimer's disease. *J. Intern. Med.* 256, 195–204.

Bäckman, L., and Small, B. J. (2007). Cognitive deficits in preclinical Alzheimer's disease and vascular dementia: patterns of findings from the Kungsholmen Project. *Physiol. Behav.* 10, 80–86.

Baldi, E., and Bucherelli, C. (2005). The inverted "u-shaped" dose-effect relationships in learning and memory: modulation of arousal and consolidation. *Nonlinearity Biol. Toxicol. Med.* 3, 9–21.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., and Jones, E. (2011). Alzheimer's disease. *Lancet* 377, 1019–1031.

Blennow, K. (2010a). Dementia in 2010: paving the way for Alzheimer disease drug development. *Nat. Rev. Neurol.* 7, 65–66.

Blennow, K. (2010b). Biomarkers in Alzheimer's disease drug development. *Nat. Med.* 16, 1218–1222.

Bordet, R., Dartigues, J. F., Dubois, B., Goehrs, J. M., Vernoux, L., Semah, F., et al. (2010). Biomarkers for the early stages of clinical development in Alzheimer's disease. *Therapie* 65, 285–290.

Bower, G. H., and Sivers, H. (1998). Cognitive impact of traumatic events. *Dev. Psychopathol.* 10, 625–653.

Brand, M., Eggers, C., Reinhold, N., Fujiwara, E., Kessler, J., Heiss, W. D., et al. (2009). Functional brain imaging in 14 patients with dissociative amnesia reveals right inferolateral prefrontal hypometabolism. *Psychiatry Res.* 174, 32–39.

Brand, M., Kalbe, E., Fujiwara, E., Huber, M., and Markowitsch, H. J. (2003). Cognitive estimation in patients with probable Alzheimer's disease and alcoholic Korsakoff patients. *Neuropsychologia* 41, 575–584.

Brandt, J., and Van Gorp, W. G. (2006). Functional ("psychogenic") amnesia. *Semin. Neurol.* 26, 331–340.

Brewin, C. R. (2011). The nature and significance of memory disturbance in posttraumatic stress disorder. *Annu. Rev. Clin. Psychol.* 7, 203–227.

Burgess, N., Maguire, E. A., and O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron* 35, 625–641.

Butters, N., Granholm, E., Salmon, D. P., Grant, I., and Wolfe, J. (1987). Episodic and semantic memory: a comparison of amnesic and demented patients. *J. Clin. Exp. Neuropsychol.* 9, 479–497.

Carcaillon, L., Amievaa, H., Auriacombea, S., Helmera, C., and Dartiguesa, J.-F. (2009). A subtest of the MMSE as a valid test of episodic memory? Comparison with the free and cued reminding test. *Dement. Geriatr. Cogn. Disord.* 27, 429–438.

Cheke, L. G., Bird, C. D., and Clayton, N. S. (2011). Tool-use and instrumental learning in the Eurasian jay (*Garrulus glandarius*). *Anim. Cogn.* 14, 441–455.

Clayton, N. S., and Dickinson, A. (1998). Episodic-like memory during cache recovery by scrub jays. *Nature* 395, 272–274.

Cravens, C. J., Vargas-Pinto, N., Christian, K. M., and Nakazawa, K. (2006). CA3 NMDA receptors are crucial for rapid and automatic representation of context memory. *Eur. J. Neurosci.* 24, 1771–1780.

Dally, J. M., Emery, N. J., and Clayton, N. S. (2006). Food-caching western scrub-jays keep track of who was watching when. *Science* 312, 1662–1665.

DeCoteau, W. E., and Kesner, R. P. (2000). A double dissociation between the rat hippocampus and medial caudoputamen in processing two forms of knowledge. *Behav. Neurosci.* 114, 1096–1108.

Dere, E., De Souza Silva, M. A., and Huston, J. P. (2004). Higher order memories for objects encountered in different spatio-temporal contexts in mice: evidence for episodic memory. *Rev. Neurosci.* 15, 231–240.

Dere, E., Frisch, C., De Souza Silva, M. A., Gödecke, A., Schrader, J., and Huston, J. P. (2001). Unaltered radial maze performance and brain acetylcholine of the endothelial nitric oxide synthase knockout mouse. *Neuroscience* 107, 561–570.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2005a). Integrated memory for objects, places and temporal order: evidence for episodic-like memory in mice. *Neurobiol. Learn. Mem.* 84, 214–221.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2005b). Protocol: episodic-like memory in mice: simultaneous assessment of object, place and temporal order memory. *Brain Res. Brain Res. Protoc.* 16, 10–19.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2007). The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. *Neurosci. Biobehav. Rev.* 31, 673–704.

Dere, E., Kart-Teke, E., Huston, J. P., and De Souza Silva, M. A. (2006). The case for episodic memory in animals. *Neurosci. Biobehav. Rev.* 30, 1206–1224.

Dere, E., Pause, B., and Pietrowsky, R. (2010). Emotion and episodic memory in neuropsychiatric disorders. *Behav. Brain Res.* 215, 162–171.

Dere, E., Zlomuzica, A., Huston, J. P., and De Souza Silva, M. A. (2008). "Chapter 2.2: animal episodic memory," in *Handbook of Episodic Memory*, Vol. 18, eds E. Dere, A. Easton, L. Nadel, and J. P. Huston (Amsterdam: Elsevier Science), 155–184.

Di Stefano, A., Iannitelli, A., Laserra, S., and Sozio, P. (2011). Drug delivery strategies for Alzheimer's disease treatment. *Expert Opin. Drug Deliv.* 8, 581–603.

Díaz-Trujillo, A., Contreras, J., Medina, A. C., Silveyra-Leon, G. A., Antaramian, A., Quirarte, G. L., et al. (2009). Enhanced inhibitory avoidance learning prevents the long-term memory-impairing effects of cycloheximide, a protein synthesis inhibitor. *Neurobiol. Learn. Mem.* 91, 310–314.

Dickerson, B. C., and Eichenbaum, H. (2010). The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology* 35, 86–104.

Donix, M., Brons, C., Jurjanz, L., Poettrich, K., Winiecki, P., and Holthoff, V. A. (2010). Overgenerality of autobiographical memory in people with amnestic mild cognitive impairement and early Alzheimer's disease. *Arch. Clin. Neuropsychol.* 25, 22–27.

Dreyfus, D. M., Roe, C. M., and Morris, J. C. (2010). Autobiographical memory task in assessing dementia. *Arch. Neurol.* 67, 862–866.

Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 6, 734–746.

Earles, J. L., Kersten, A. W., Curtayne, E. S., and Perle, J. G. (2008). That's the man who did it, or was it a woman? Actor similarity and binding errors in event memory. *Psychon. Bull. Rev.* 15, 1185–1189.

Ebenezer, I. S. (1988). Can vasopressin alone act as an unconditioned stimulus to produce passive avoidance behaviour in rats in a typical memory experiment? *Neuropharmacology* 27, 903–907.

Ehrlichman, H., and Halpern, J. N. (1988). Affect and memory: effects of pleasant and unpleasant odors on retrieval of happy and unhappy memories. *J. Pers. Soc. Psychol.* 55, 769–779.

Emery, N. J., and Clayton, N. S. (2004). The mentality of crows: convergent evolution of intelligence in corvids and apes. *Science* 306, 1903–1907.

Ennaceur, A. (2010). One-trial object recognition in rats and mice: methodological and theoretical issues. *Behav. Brain Res.* 215, 244–254.

Fine, E. M., Delis, D. C., Wetter, S. R., Jacobson, M. W., Hamilton, J. M., Peavy, G., et al. (2008). Identifying the "source" of recognition memory deficits in patients with Huntington's disease or Alzheimer's disease: evidence from the CVLT-II. *J. Clin. Exp. Neuropsychol.* 30, 463–470.

Friedman, W. J. (1996). "Distance and location processes in the memory for the times of past events," in *The Psychology of Learning and Motivation*, Vol. 35, ed. D. L. Medin (San Diego: Academic Press), 1–41.

Fouquet, C., Petit, G. H., Auffret, A., Gaillard, E., Rovira, C., Mariani, J., et al. (2011). Early detection of age-related memory deficits in individual mice. *Neurobiol. Aging* 32, 1881–1895.

Fouquet, C., Tobin, C., and Rondi-Reig, L. (2010). A new approach for modeling episodic memory from rodents to humans: the temporal order memory. *Behav. Brain Res.* 215, 172–179.

Fulton, D., Kemenes, I., Andrew, R. J., and Benjamin, P. R. (2005). A single time-window for protein synthesis-dependent long-term memory formation after one-trial appetitive conditioning. *Eur. J. Neurosci.* 21, 1347–1358.

Galluzzi, S., and Frisoni, G. B. (2008). Imaging, subjective complaints, and MCI: 30 years before. *J. Nutr. Health Aging* 12, 80S–83S.

Gilboa, A., Ramirez, J., Köhler, S., Westmacott, R., Black, S. E., and Moscovitch, M. (2005). Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. *Hippocampus* 15, 535–550.

Griffiths, D. P., and Clayton, N. S. (2001). Testing episodic memory in animals: a new approach. *Physiol. Behav.* 73, 755–762.

Grober, E., and Buschke, H. (1987). Genuine memory deficits in dementia. *Dev. Neuropsychol.* 3, 13–36.

Grodzinski, U., and Clayton, N. S. (2010). Problems faced by food-caching corvids and the evolution of cognitive solutions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 365, 977–987.

Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* 2, 289–293.

Hampel, H., Frank, R., Broich, K., Teipel, S. J., Katz, R. G., Hardy, J., et al. (2010). Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nat. Rev. Drug Discov.* 9, 560–574.

Humphreys, M. S., Smith, S., Pachana, N. A., Tehan, G., and Byrne, G. J. (2010). Measuring episodic memory: a novel approach with an indefinite number of alternative forms. *Appl. Cogn. Psychol.* 24, 1080–1094.

Hurlemann, R., Wagner, M., Hawellek, B., Reich, H., Pieperhoff, P., Amunts, K., et al. (2007). Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe disease. *Neuropsychologia* 45, 877–884.

Igaz, L. M., Vianna, M. R., Medina, J. H., and Izquierdo, I. (2002). Two time

periods of hippocampal mRNA synthesis are required for memory consolidation of fear-motivated learning. *J. Neurosci.* 22, 6781–6789.

Irish, M., Lawlor, B. A., O'Mara, S. M., and Coen, R. F. (2011). Impaired capacity for autonoetic reliving during autobiographical event recall in mild Alzheimer's disease. *Cortex* 47, 236–249.

Kapur, N. (1991). Amnesia in relation to fugue states – distinguishing a neurological from a psychogenic basis. *Br. J. Psychiatry* 159, 872–877.

Kart-Teke, E., De Souza Silva, M. A., Huston, J. P., and Dere, E. (2006). Wistar rats show episodic-like memory for unique experiences. *Neurobiol. Learn. Mem.* 85, 173–182.

Kensinger, E. A., Addis, D. R., and Atapattu, R. K. (2011). Amygdala activity at encoding corresponds with memory vividness and with memory for select episodic details. *Neuropsychologia* 49, 663–673.

Kinugawa, K., Schumm, S., Pollina, M., Depre, M., Jungbluth, C., Doulazmi, M., et al. (2013). Aging-related episodic memory decline: are emotions the key? *Front. Behav. Neurosci.* 7:2. doi:10.3389/fnbeh.2013.00002

Kirchhoff, B. A., Wagner, A. D., Maril, A., and Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J. Neurosci.* 20, 6173–6180.

Klein, S. B. (2013). Making the case that episodic recollection is attributable to operations occurring at retrieval rather than to content stored in a dedicated subsystem of long-term memory. *Front. Behav. Neurosci.* 7:3. doi:10.3389/fnbeh.2013.00003

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.* 11, 724–744.

Laudien, J. H., Wencker, S., Ferstl, R., and Pause, B. M. (2008). Context effects on odor processing: an event-related potential study. *Neuroimage* 41, 1426–1436.

Lehmann, H., Lacanilao, S., and Sutherland, R. J. (2007). Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *Eur. J. Neurosci.* 25, 1278–1286.

Lekeu, F., Magis, D., Marique, P., Delbeuck, X., Bechet, S., Guillaume, B., et al. (2010). The California Verbal Learning Test and other standard clinical neuropsychological tests to predict conversion from mild memory impairment to dementia. *J. Clin. Exp. Neuropsychol.* 32, 164–173.

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol. Aging* 17, 677–689.

Lezak, M. D. (1995). *Neuropsychological Assessment*, 3rd Edn. New York: Oxford University Press.

Li, J. S., Hsiao, K. Y., and Chen, W. M. (2011). Effects of medial prefrontal cortex lesions in rats on the what-where-when memory of a fear conditioning event. *Behav. Brain Res.* 218, 94–98.

Libkuman, T. M., Stabler, C. L., and Otani, H. (2004). Arousal, valence, and memory for detail. *Memory* 12, 237–247.

Light, L. L., and Albertson, S. A. (1989). Direct and indirect tests of memory for category exemplars in young and older adults. *Psychol. Aging* 4, 487–492.

Lima, R. H., Rossato, J. I., Furini, C. R., Bevilaqua, L. R., Izquierdo, I., and Cammarota, M. (2009). Infusion of protein synthesis inhibitors in the entorhinal cortex blocks consolidation but not reconsolidation of object recognition memory. *Neurobiol. Learn. Mem.* 91, 466–472.

Madan, C. R., and Singhal, A. (2012). Using actions to enhance memory: effects of enactment, gestures, and exercise on human memory. *Front. Psychol.* 3:507. doi:10.3389/fpsyg.2012.00507

Markowitsch, H. J., Calabrese, P., Fink, G. R., Durwen, H. F., Kessler, J., Härting, C., et al. (1997). Impaired episodic memory retrieval in a case of probable psychogenic amnesia. *Psychiatry Res.* 74, 119–126.

Markowitsch, H. J., and Staniloiu, A. (2011). Amygdala in action: relaying biological and social significance to autobiographical memory. *Neuropsychologia* 49, 718–733.

Martinelli, P., Anssens, A., Sperduti, M., and Piolino, P. (2013). The influence of normal aging and Alzheimer's disease in autobiographical memory highly related to the self. *Neuropsychology* 27, 69–78.

Masaoka, Y., Sugiyama, H., Katayama, A., Kashiwagi, M., and Homma, I. (2012). Slow breathing and emotions associated with odor-induced autobiographical memories. *Chem. Senses* 37, 379–388.

McCabe, D. P., Roediger, H. L. III, and Karpicke, J. D. (2011). Automatic processing influences free recall: converging evidence from the process dissociation procedure and remember-know judgments. *Mem. Cognit.* 39, 389–402.

McKenzie, S., and Eichenbaum, H. (2011). Consolidation and reconsolidation: two lives of memories? *Neuron* 71, 224–233.

Mitchell, J. B., and Laiacona, J. (1998). The medial frontal cortex and temporal memory: tests using spontaneous exploratory behaviour in the rat. *Behav. Brain Res.* 97, 107–113.

Murphy, K. J., Troyer, A. K., Levine, B., and Moscovitch, M. (2008). Episodic, but not semantic, autobiographical memory is reduced in amnestic mild cognitive impairment. *Neuropsychologia* 46, 3116–3123.

Nashiro, K., and Mather, M. (2011). How arousal affects younger and older adults' memory binding. *Exp. Aging Res.* 37, 108–128.

Nordberg, A., Rinne, J. O., Kadir, A., and Långström, B. (2010). The use of PET in Alzheimer disease. *Nat. Rev. Neurol.* 6, 78–87.

Nyberg, L., McIntosh, A. R., Houle, S., Nilsson, L. G., and Tulving, E. (1996). Activation of medial temporal structures during episodic memory retrieval. *Nature* 380, 715–717.

Oliveira, M. G., Bueno, O. F., Pomarico, A. C., and Gugliano, E. B. (1997). Strategies used by hippocampal- and caudate-putamen-lesioned rats in a learning task. *Neurobiol. Learn. Mem.* 68, 32–41.

Pause, B., Jungbluth, C., Adolph, D., Pietrowsky, R., and Dere, E. (2010). Induction and measurement of episodic memories in healthy adults. *J. Neurosci. Methods* 189, 88–96.

Pause, B. M., Hellmann, G., Göder, R., Aldenhoff, J. B., and Ferstl, R. (2008). Increased processing speed for emotionally negative odors in schizophrenia. *Int. J. Psychophysiol.* 70, 16–22.

Pennartz, C. M. (2009). Identification and integration of sensory modalities: neural basis and relation to consciousness. *Conscious. Cogn.* 18, 718–739.

Pettersson, M., Kauffman, G. W., Ende, C. W., Patel, N. C., Stiff, C., Tran, T. P., et al. (2011). Novel γ-secretase modulators: a review of patents from 2008 to 2010. *Expert Opin. Ther. Pat.* 21, 205–226.

Phelps, E. A., Labar, K. S., Anderson, A. K., O'Connor, K. J., Fulbright, R. K., and Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: a case study. *Neurocase* 6, 527–540.

Pike, K. E., and Savage, G. (2008). Memory profiling in mild cognitive impairment: can we determine risk for Alzheimer's disease? *J. Neuropsychol.* 2, 361–372.

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329.

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., and Piolino, P. (2012a). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia* 50, 592–602.

Plancher, G., Barra, J., Orriols, E., and Piolino, P. (2012b). The influence of action on episodic memory: a virtual reality study. *Q. J. Exp. Psychol. (Hove)*. (in press).

Pöppel, E. (1997). A hierarchical model of temporal perception. *Trends Cogn. Sci. (Regul. Ed.)* 1, 56–61.

Raby, C. R., Alexis, D. M., Dickinson, A., and Clayton, N. S. (2007). Planning for the future by western scrub-jays. *Nature* 445, 919–921.

Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus* 20, 1263–1290.

Rattenborg, N. C., and Martinez-Gonzalez, D. (2011). A bird-brain view of episodic memory. *Behav. Brain Res.* 222, 236–245.

Reinhold, N., and Markowitsch, H. J. (2009). Retrograde episodic memory and emotion: a perspective from patients with dissociative amnesia. *Neuropsychologia* 47, 2197–2206.

Reitz, C., Tang, M. X., Schupf, N., Manly, J. J., Mayeux, R., and Luchsinger, J. A. (2010). A summary risk score for the prediction of Alzheimer disease in elderly persons. *Arch. Neurol.* 67, 835–841.

Ringman, J. M. (2005). What the study of persons at risk for familial Alzheimer's disease can tell us about the earliest stages of the disorder: a review. *J. Geriatr. Psychiatry Neurol.* 18, 228–233.

Roberts, W. A. (2002). Are animals stuck in time? *Psychol. Bull.* 128, 473–489.

Roberts, W. A., Feeney, M. C., MacPherson, K., Petter, M., McMillan, N., and Musolino, E. (2008). Episodic-like memory in rats: is it based on

when or how long ago? *Science* 320, 113–115.

Rondi-Reig, L., Petit, G. H., Tobin, C., Tonegawa, S., Mariani, J., and Berthoz, A. (2006). Impaired sequential egocentric and allocentric memories in forebrain-specific-NMDA receptor knock-out mice during a new task dissociating strategies of navigation. *J. Neurosci.* 26, 4071–4081.

Rossato, J. I., Bevilaqua, L. R., Myskiw, J. C., Medina, J. H., Izquierdo, I., and Cammarota, M. (2007). On the role of hippocampal protein synthesis in the consolidation and reconsolidation of object recognition memory. *Learn. Mem.* 14, 36–46.

Rudy, J. W., Huff, N. C., and Matus-Amat, P. (2004). Understanding contextual fear conditioning: insights from a two-process model. *Neurosci. Biobehav. Rev.* 28, 675–685.

Rudy, J. W., and Sutherland, R. J. (1995). Configural association theory and the hippocampal formation: an appraisal and reconfiguration. *Hippocampus* 5, 375–389.

Saive, A.-L., Ravel, N., Thévenet, M., Royet, J.-P., and Plailly, J. (2013). A novel experimental approach to episodic memory in humans based on the privileged access of odors to memories. *J. Neurosci. Methods* 213, 22–31.

Salwiczek, L. H., Emery, N. J., Schlinger, B., and Clayton, N. S. (2009). The development of caching and object permanence in Western scrub-jays (*Aphelocoma californica*): which emerges first? *J. Comp. Psychol.* 123, 295–303.

Sara, S. J., David-Remacle, M., and Lefevre, D. (1975). Passive avoidance behavior in rats after electroconvulsive shock: facilitative effect of response retardation. *J. Comp. Physiol. Psychol.* 89, 489–497.

Sarazin, M., and Dubois, B. (2005). A guide to diagnosis of Alzheimer's disease. *Rev. Prat.* 55, 1879–1890.

Schacter, D. L., Norman, K. A., and Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annu. Rev. Psychol.* 49, 289–318.

Schafe, G. E., Nadel, N. V., Sullivan, G. M., Harris, A., and LeDoux, J. E. (1999). Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase activity. *Learn. Mem.* 6, 97–110.

Schwindt, G. C., and Black, S. E. (2009). Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. *Neuroimage* 45, 181–190.

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S. C., and Lindenberger, U. (2010). Episodic memory across the lifespan: the contributions of associative and strategic components. *Neurosci. Biobehav. Rev.* 34, 1080–1091.

Small, B. J., and Bäckman, L. (2007). Longitudinal trajectories of cognitive change in preclinical Alzheimer's disease: a growth mixture modeling analysis. *Cortex* 43, 826–834.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol. Learn. Mem.* 82, 171–177.

Squire, L. R., and Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177.

Tagini, A., and Raffone, A. (2010). The 'I' and the 'Me' in self-referential awareness: a neurocognitive hypothesis. *Cogn. Process.* 11, 9–20.

Thomas-Anterion, C., and Laurent, B. (2006). Neuropsychological markers for the diagnosis of Alzheimer's disease. *Rev. Neurol. (Paris)* 162, 913–920.

Trojanowski, J. Q., Vandeerstichele, H., Korecka, M., Clark, C. M., Aisen, P. S., Petersen, R. C., et al. (2010). Update on the biomarker core of the Alzheimer's disease neuroimaging initiative subjects. *Alzheimers Dement.* 6, 230–238.

Tronche, C., Lestage, P., Louis, C., Carrie, I., and Béracochéa, D. (2010). Pharmacological modulation of contextual "episodic-like" memory in aged mice. *Behav. Brain Res.* 215, 255–260.

Tsirka, P., Simos, A., Vakis, M., Vourkas, V., Arzoglou, N., Syrmos, S., et al. (2010). Material-specific difficulties in episodic memory tasks in mild traumatic brain injury. *Int. J. Neurosci.* 120, 184–191.

Tsivilis, D., Vann, S. D., Denby, C., Roberts, N., Mayes, A. R., Montaldi, D., et al. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nat. Neurosci.* 11, 834–842.

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–403.

Tulving, E. (1983). *Elements of Episodic Memory*. London: Oxford University Press.

Tulving, E. (2001). Episodic memory and common sense: how far apart? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1505–1515.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25.

Unsworth, N., Brewer, G. A., and Spillers, G. J. (2011). Inter- and intra-individual variation in immediate free recall: an examination of serial position functions and recall initiation strategies. *Memory* 19, 67–82.

Urbaniak-Hunter, K., Yarbrough, C., and Ciacci, J. (2010). Gene- and cell-based approaches for neurodegenerative disease. *Adv. Exp. Med. Biol.* 671, 117–130.

van der Hart, O., and Nijenhuis, E. (2001). Generalized dissociative amnesia: episodic, semantic and procedural memories lost and found. *Aust. N. Z. J. Psychiatry* 35, 589–600.

van Rossum, I. A., Vos, S., Handels, R., and Visser, P. J. (2010). Biomarkers as predictors for conversion from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. *J. Alzheimers Dis.* 20, 881–891.

Wagner, A. D. (2000). Early detection of Alzheimer's disease: an fMRI marker for people at risk? *Nat. Neurosci.* 3, 973–974.

Walker, M. P., Brakefield, T., Hobson, J. A., and Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425, 616–620.

Weiner, H. L., and Frenkel, D. (2006). Immunology and immunotherapy of Alzheimer's disease. *Nat. Rev. Immunol.* 6, 404–416.

Wiest, G., Lehner-Baumgartner, E., and Baumgartner, C. (2006). Panic attacks in an individual with bilateral selective lesions of the amygdala. *Arch. Neurol.* 63, 1798–1801.

Williams-Gray, C. H., Foltynie, T., Lewis, S. J., and Barker, R. A. (2006). Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options. *CNS Drugs* 20, 477–505.

Wolff, M., Loukavenko, E. A., Will, B. E., and Dalrymple-Alford, J. C. (2008). The extended hippocampal-diencephalic memory system: enriched housing promotes recovery of the flexible use of spatial representations after anterior thalamic lesions. *Hippocampus* 18, 996–1007.

Woodard, J. L., Goldstein, F. C., Roberts, V. J., and McGuire, C. (1999). Convergent and discriminant validity of the CVLT (dementia version). California Verbal Learning Test. *J. Clin. Exp. Neuropsychol.* 21, 553–558.

Yankner, B. A. (1996a). New clues to Alzheimer's disease: unraveling the roles of amyloid and tau. *Nat. Med.* 2, 850–852.

Yankner, B. A. (1996b). Mechanisms of neuronal degeneration in Alzheimer's disease. *Neuron* 16, 921–932.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517.

Zentall, T. R., Singer, R. A., and Stagner, J. P. (2008). Episodic-like memory: pigeons can report location pecked when unexpectedly asked. *Behav. Processes* 79, 93–98.

Zimmer, H. D., Speiser, H. R., and Seidler, B. (2003). Spatio-temporal working-memory and short-term object-location tasks use different memory mechanisms. *Acta Psychol. (Amst.)* 114, 41–65.

Zlomuzica, A., De Souza Silva, M. A., Huston, J. P., and Dere, E. (2007). NMDA receptor modulation by D-cycloserine promotes episodic-like memory in mice. *Psychopharmacology* 193, 503–509.

Zlomuzica, A., Dere, E., Huston, J. P., and de Souza Silva, M. A. (2008). NK(3) receptor agonism promotes episodic-like memory in mice. *Neurobiol. Learn. Mem.* 90, 420–425.

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Competitive trace theory: a role for the hippocampus in contextual interference during retrieval

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Much controversy exists regarding the role of the hippocampus in retrieval. The two dominant and competing accounts have been the Standard Model of Systems Consolidation (SMSC) and Multiple Trace Theory (MTT), which specifically make opposing predictions as to the necessity of the hippocampus for retrieval of remote memories. Under SMSC, memories eventually become independent of the hippocampus as they become more reliant on cortical connectivity, and thus the hippocampus is not required for retrieval of remote memories, only recent ones. MTT on the other hand claims that the hippocampus is always required no matter the age of the memory. We argue that this dissociation may be too simplistic, and a continuum model may be better suited to address the role of the hippocampus in retrieval of remote memories. Such a model is presented here with the main function of the hippocampus during retrieval being "recontextualization," or the reconstruction of memory using overlapping traces. As memories get older, they are decontextualized due to competition among partially overlapping traces and become more semantic and reliant on neocortical storage. In this framework dubbed the Competitive Trace Theory (CTT), consolidation events that lead to the strengthening of memories enhance conceptual knowledge (semantic memory) at the expense of contextual details (episodic memory). As a result, remote memories are more likely to have a stronger semantic representation. At the same time, remote memories are also more likely to include illusory details. The CTT is a novel candidate model that may provide some resolution to the memory consolidation debate.

Keywords: systems consolidation, multiple trace theory, pattern separation, pattern completion, interference, episodic memory, semantic memory, competition

INTRODUCTION

Much evidence points to the significant role of the hippocampus in the encoding of new declarative memories (Milner et al., 1998; Squire, 2009). This small region of the brain possesses a unique architecture that allows it to rapidly encode experiences while minimizing interference. Virtually every model of learning ascribes this important function to the hippocampus, especially in the context of declarative memory (in contrast to habit or other procedural learning). However, the role of the hippocampus in retrieval (especially episodic retrieval) is still subject to debate. While there is certainly a neural architecture in the hippocampus capable of such contextual retrieval, for example, a recurrent collateral network in CA3 capable of autoassociation (Marr, 1971), as well as an abundance of evidence across species demonstrating the involvement of the hippocampus in contextual retrieval tasks (Eldridge et al., 2000; Ryan et al., 2001; Yonelinas et al., 2002, 2005; Holdstock et al., 2004; Daselaar et al., 2006; Diana et al., 2007; Wiltgen et al., 2010; Goshen et al., 2011) there is still an active debate about whether the hippocampus is required for retrieval of *remote* episodic memories.

SYSTEMS CONSOLIDATION VS. MULTIPLE TRACE THEORY

At present, two major theories make predictions relevant to this debate. The first is the Standard Model of Systems Consolidation (SMSC: Squire and Alvarez, 1995), a widely influential view in the field. The SMSC holds that the initial memory trace is encoded both in the hippocampus and in the cortex, though the cortex is itself unable to initially support the memory. Rather, the hippocampus is critical in early encoding stages. As a function of time, replay, and retrieval, the hippocampus "teaches" the cortex the memory trace such that the associative connectivity between the individual elements of the cortical memory increase in strength over time. After the memory has been consolidated, the hippocampus is no longer required for retrieval. This is based on the large body of evidence that synapses change much more rapidly and dynamically in the hippocampus than they do in cortex (Frankland and Bontempi, 2005). These ideas were first proposed by Marr (1971) and further elaborated by the widely influential Complementary Learning Systems (CLS) model of McClelland et al. (1995), which emphasizes the role of hippocampal-neocortical interactions in the formation and consolidation of memory. Thus, the SMSC predicts that the hippocampus is not required for the retrieval of remote memories, only recent ones that have not yet been fully consolidated.

The competing theory, known as Multiple Trace Theory (MTT), was proposed by Nadel and Moscovitch (1997) as an alternative to the standard model. Unlike the SMSC, MTT proposed that the hippocampus has an important role in the retrieval of all episodic memories, including remote ones. Similar to the SMSC, MTT also proposed that memories are encoded in

hippocampal-neocortical networks, but that each reactivation resulted in a different trace in the hippocampus. Hippocampal-bound traces are presumed to be contextual and rich in spatial and temporal details, while cortical-bound traces are presumed to be semantic and largely context-free. Thus, retrieval of remote semantic memories does not require the hippocampus, however, retrieval of remote episodic memories always does, irrespective of the age of the memory.

Thus, at the heart of the debate is the role of the hippocampus in the retrieval of remote episodic memories. In fact, that has been the only reliably testable prediction for either theory thus far, although as discussed below, support for even this single prediction proved tenuous at best. First, it is important to recognize that both models were proposed to explain amnesia data from human and animal studies, and namely the nature of the retrograde amnesia (RA) gradient observed. While numerous studies have observed that the RA gradient was temporally graded, in many cases, the RA gradient was flat, and in some cases the degree of RA gradient depended on the size of the lesion (reviewed in Frankland and Bontempi, 2005). In addition to lesion data, data from functional magnetic resonance imaging (fMRI) has been brought to bear on this debate. For example, Nadel and Moscovitch (1997) have shown that medial temporal fMRI activity was equally predictive of recent and remote memory retrieval. However, a major criticism of these studies is that the hippocampus is involved in incidental and automatic encoding during retrieval tasks, which may obscure retrieval-related activity (Buckner et al., 2001; Haist et al., 2001; Stark and Okado, 2003). A recent survey of the evidence based on amnesia studies in rodents with partial and full hippocampal damage provides overwhelming support for flat RA gradients, which argues against the SMSC (cf. Sutherland et al., 2010). Importantly, however, these data also argue against one prediction of MTT, which is that *partial* hippocampal damage will lead to a temporal RA gradient. Thus, neither model can adequately account for lesion data in animals.

Two particularly compelling pieces of data are worth discussing here to further illustrate the complexity of this debate. Scoville and Milner (1957) initially reported that patient H. M. had a case of temporally graded RA. In fact, much of the subsequent work on RA was based on this initial finding. Much later, however, as it became clearer that neuropsychological testing procedures were not as refined in that era and that episodic memory could not have been tested fully. Corkin (2002) later asserted that "H. M. was unable to supply an episodic memory of his mother or his father – he could not narrate even one event that occurred at a specific time and place." She surmised that many of the remote memories H. M. was able to retrieve were indeed "semanticized." In contrast, patient E. P., another case of profound amnesia studied by Squire and colleagues, was able to demonstrate highly detailed spatial remote memories (Stefanacci et al., 2000), arguing against the notion of a flat episodic RA gradient. This is further complicated by the inconsistency of results across studies of different amnesic patients with partial medial temporal lobe or hippocampal damage, and the lack of detailed neuroanatomical quantification in many cases. Thus, evidence from amnesia as to the RA gradient is not entirely conclusive, and provides only partial and sometimes conflicting support for either of the major theories discussed above.

A recent study by Goshen et al. (2011) used optogenetic techniques to demonstrate that hippocampal CA1 neuron activation was necessary for the retrieval of several week old (i.e., remote) memories, providing evidence against the SMSC. However, they also showed that longer inhibition (matching the timescale of the more typical pharmacological inhibition) abolished this dependence on the hippocampus, weakening the account provided by MTT. While Goshen and colleagues suggested that there is compensation via other structures such as the anterior cingulate cortex, the data can be taken to suggest both MTT and SMSC may both be at work and that perhaps each offers elements of the true nature of memory consolidation. This recent work motivates and underscores the value of alternate proposals that attempt to harmonize between the two models.

THE HIPPOCAMPUS AS AN INDEX

Both accounts discussed above rely to an extent on the notion of hippocampal indexing. These ideas were initially presented by Teyler and DiScenna (1985), and were formally developed into the hippocampal memory indexing theory (Teyler and DiScenna, 1986). This theory has served as a critical component of our current understanding of hippocampal computations, and as such, it warrants discussion here (for review, see Teyler and Rudy, 2007).

The central aim of the hippocampal memory indexing theory is to explain the nature of hippocampal involvement in encoding and retrieving memory traces. Particularly, this was among the first attempts at explaining interactions between the hippocampus and neocortex during episodic memory computations. Though evidence had accumulated to underscore the importance of the hippocampus in many memory processes, two important realizations came to light. First, there appeared to be multiple neural networks capable of supporting memory (Sherry and Schacter, 1987). Second, the neocortex itself was found to be sufficient to support some aspects of memory (Squire et al., 1984). Tulving and Markowitsch (1998) went on to propose that episodic memory – that is, memory rich in associated contextual details – is especially dependent on the hippocampus. Indexing theory describes the involvement and ultimate fate of these contextual details.

According to this theory, when a memory trace is encoded, inputs from cortical sensory regions activate a relatively small population of hippocampal synapses. The hippocampus in turn activates a network of neocortical regions, and as the memory is consolidated, the connections between the hippocampus and neocortex are strengthened. Laying down hippocampal-neocortical connections in this manner creates a physical instantiation of the memory trace. Importantly, the hippocampus here plays a pivotal role in memory retrieval. Activation of a small subset of neocortical regions, part of a larger pattern comprising a consolidated memory trace, can signal the hippocampus to re-instantiate the full pattern despite partial or degraded input. In short, this provides an account for how certain aspects or contextual details of an event can lead to recall of other related details.

It deserves further emphasis that under this interpretation, the hippocampus does not store details about an event *per se*, but as the name of the theory implies, rather acts as an index. That is, as was described in Teyler and DiScenna's theory, the hippocampus is proposed to serve in coupling the activity of neocortical

regions such that patterns of activity can induce recall of a given memory trace. To make this proposition as clear as possible, let us consider another description. If information is stored across the neocortex, we might imagine it as a library. Memories, much like library books, are often added, removed, or replaced. When reconstructing an experience, one may need to access information residing in different wings of the library. This is where the hippocampus, our trusty librarian, comes in. While it has not stored the wealth of knowledge contained in the library in a way that it can readily reproduce, it can point to the correct locations where this knowledge can be retrieved.

COMPETITIVE TRACE THEORY

We propose an alternative to the current theories of recent and remote memory that combines elements of SMSC and MTT largely within the framework of indexing theory. The account, which we will refer to as the competitive trace theory (CTT), is an integrated theory that attempts to explain phenomenological distinctions such as episodic vs. semantic, using neurocomputational proposals based on interference and associations.

CONSOLIDATION AND DECONTEXTUALIZATION

First, we will start with some operational definitions. The words "episodic" and "semantic" have been used abundantly in the memory literature to refer to memories that are rich in contextual detail and memories that are devoid of such details, respectively. However, there is an additional important distinction that should be considered here. That is the accuracy of such memory, which is often uncorrelated with the success of recollection (Gallo et al., 2001; Roediger et al., 2004; Kensinger and Schacter, 2007; Stahl and Klauer, 2008; Kim and Yassa, 2013). Thus, in the CTT framework, the word "episodic" will only be used to describe the phenomenological experience of contextual recollection and not in reference to the accuracy of the memory. Inherent in this assignment is the strong claim that these labels ("recollection" and "episodic") are only helpful insofar as they describe the experience and not describe the memory representation itself, which is far more dynamic and often contains illusory details.

The word "semantic," on the other hand, will be used to refer to the accurate knowledge that builds up over time and with much repetition. The use of these terms will become more defined as we describe the central tenets of the model, and we will maintain that their use is only helpful in relative terms and not absolutes (i.e., one memory can be *more episodic than* another, but should not be labeled as "episodic" absent a frame of reference). For now, it is important to bear in mind three crucial assumptions of CTT: (1) memories are most episodic *and* veridical at the moment they are first encoded, (2) with every subsequent reactivation, the memory can become less episodic, and accurate details can be replaced with illusory details, and (3) central features of experiences become simultaneously consolidated and decontextualized (lose associated details) over time.

How does this occur? We suggest that when a memory is reactivated by an internal or external cue, the hippocampus acts to re-instantiate the neural signature of the original memory trace. In doing so, the hippocampus effectively recombines the elements of the original memory trace. Critically, the central features of that memory trace are reactivated. However, unlike prior theories of episodic memory retrieval, we propose that this process potentially adds or subtracts individual contextual features. Given the reactivation of the central features of the memory trace, the new memory significantly overlaps with the original. However, some of the features are non-overlapping, which leads to a slightly altered version of the memory. This altered memory is now capable of being stored as a new memory trace and undergoes the same storage process as the original memory. This in some ways is reminiscent of MTT, but with several important distinctions. According to our proposal, these memories are not stored in parallel, but rather compete for representation in the neocortex. Also, MTT hypothesizes that the memory traces themselves are stored in the hippocampus and not in the neocortex (this is the logic behind the "larger lesions knock out older memories" effect (Nadel and Moscovitch, 1998). Neocortical traces, according to MTT, are overlapping only insofar as the encoding and retrieval contexts are overlapping, which allows for contextual retrieval driven by hippocampal or neocortical traces. CTT, on the other hand, hypothesizes that the hippocampus itself is not the site of trace storage but rather it links the individual components of a neocortical memory together such that it can be retrieved later by the hippocampus or by the neocortex directly. Furthermore, neocortical traces themselves become devoid of context with increasing reactivations.

Two distinct phenomena can occur here: consolidation and decontextualization. First, overlapping features in the memories should not compete for representation and thus are strengthened (i.e., consolidated) in a Hebbian fashion. As a result of repeated activations, these overlapping features have a higher likelihood of being retrieved with high fidelity. The increase in associative connectivity over time allows these personal semantic components of the memory to become hippocampus-independent. That is, the overlapping neocortical components of such a memory trace have become strengthened to the extent that the hippocampus is no longer necessary to couple their activity. Second, the non-overlapping features should compete with one another resulting in mutual inhibition in an anti-Hebbian fashion, and a reduced likelihood of any of such features being retrieved. In other words, memories become decontextualized.

It follows from the above that retrieval of remote memories appears episodic and contextual because of hippocampal reconstruction and re-encoding, rather than a reactivation of a veridical representation. Without the presence of the hippocampus during retrieval (as in amnesia), the only retrievable memory is the high fidelity semantic representation in the neocortex (see **Figure 1**). These highly semanticized memories, having been consolidated and reconsolidated, are likely to feature a core set of important facts but little contextual depth. Thus, CTT can be viewed as a harmonization of SMSC and MTT in which consolidation and hippocampal independence occurs for semantic components of experiences via a multiple trace mechanism, provided that the non-overlapping portions of these traces compete for representation.

The CTT model asserts that recent episodic memories and remote episodic memories, although they share phenomenological features such as the sense of recollection or mental time

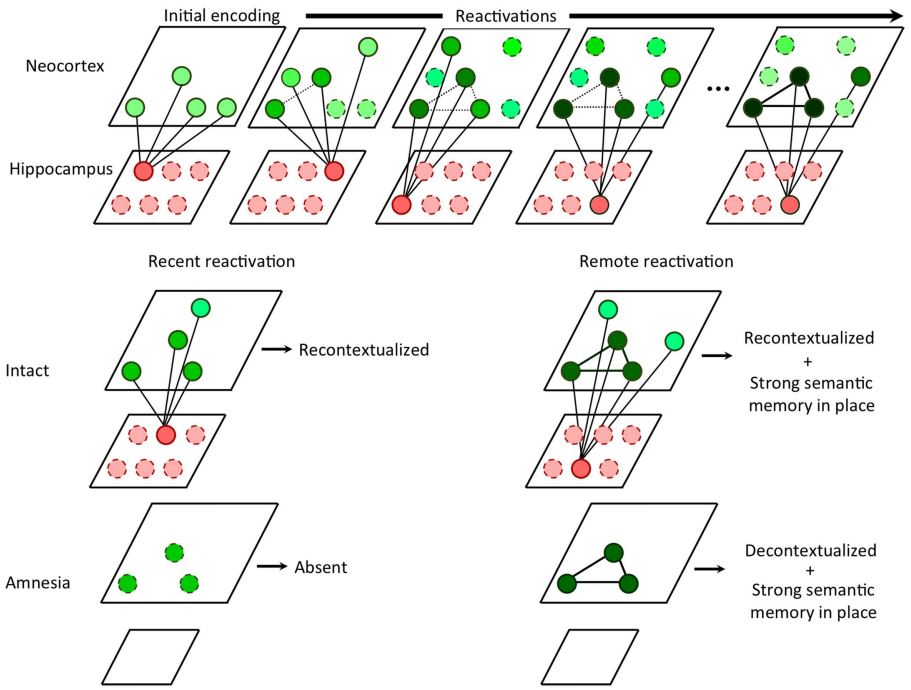


FIGURE 1 | Hippocampal competitive trace theory. Every time a memory is reactivated, the hippocampus encodes a partially overlapping trace that serves to compete with other similar traces from other reactivations in the neocortex. In the hippocampus, traces are non-overlapping due to pattern separation. In the neocortex, the overlapping features are strengthened (i.e., consolidated) while the non-overlapping features become decontextualized. During recent memory reactivation, an intact hippocampus is able to recontextualizes the memory, storing an additional trace. In amnesia, the recent memory cannot be retrieved in the absence of the hippocampus, since no features have yet been consolidated. During remote memory reactivation, an intact hippocampus continues to recontextualizes the memory, however, a strong consolidated semantic memory is in place due to a number of prior reactivations. In amnesia, the remote memory can be retrieved at least in part based on the semantic memory. Absent the hippocampus, recontextualization can no longer occur and additionally, the retrieval experience may be less contextual than that of an intact subject.

travel (Suddendorf and Corballis, 1997), possess underlying representations that could not be more different. A recent memory has no semantic components as those take time and repeated instances of remembering to build, but it is rich in accurate contextual detail. A remote memory, on the other hand, has a strong semantic component as a result of repeated retrieval events, but also contains degraded contextual information, or reconstructed contextual details that are often inaccurate.

Given these assumptions, we can redefine systems consolidation as the selective strengthening of the core content of the memory in neocortical circuits via hippocampal-neocortical interactions, coupled with a selective weakening of irrelevant and highly variable contextual details associated with each reactivation of the memory. It is important to note that the second condition of consolidation is most directly observable in hippocampal amnesia as the presence of the hippocampus in the intact brain gives the illusion of intact contextual detail, while in fact this experience is the direct result of mnemonic reconstruction and retrieval of illusory contextual details (**Figure 1**).

This raises the question of why the hippocampus continues to manufacture these illusory recollections, while a perfectly intact semantic memory is accessible in the neocortex. There are several potential answers. First, it is likely that contextual recollection, despite its inaccuracy, facilitates social interactions, and the sharing of experiences for the purpose of social bond formation. Second, reconstructing such details, which become influenced by cultural and other personal biases, may serve the important adaptive role of creating narratives that can influence others' behavior. Imagine, for example, how compelling reading someone's autobiography can be. Of course, another alternative is that there is no evolutionary advantage to recollection aside from facilitating the competition that is used to abstract memories so that massive amounts of information can be stored. In this sense, it may better facilitate learning and future adaptive behavior to incorporate illusory details into a memory than to simply forego details altogether, and the recollective experience may be nothing more than an epiphenomenon of an otherwise adaptive system.

THE RECONTEXTUALIZATION CONTINUUM

Figure 2 illustrates the episodic-semantic memory continuum (purely based on the retrieval experience, not taking into consideration the accuracy of memory). Given the slow cortical dynamics responsible for consolidation, this relationship is best represented as a continuum of decontextualization/recontextualization. In other words, the axis of this continuum is the degree of contextual detail (a function of reactivation events), which can be formally quantified. The hippocampus, at the very left of the continuum, is a context-encoding, associative device that simultaneously

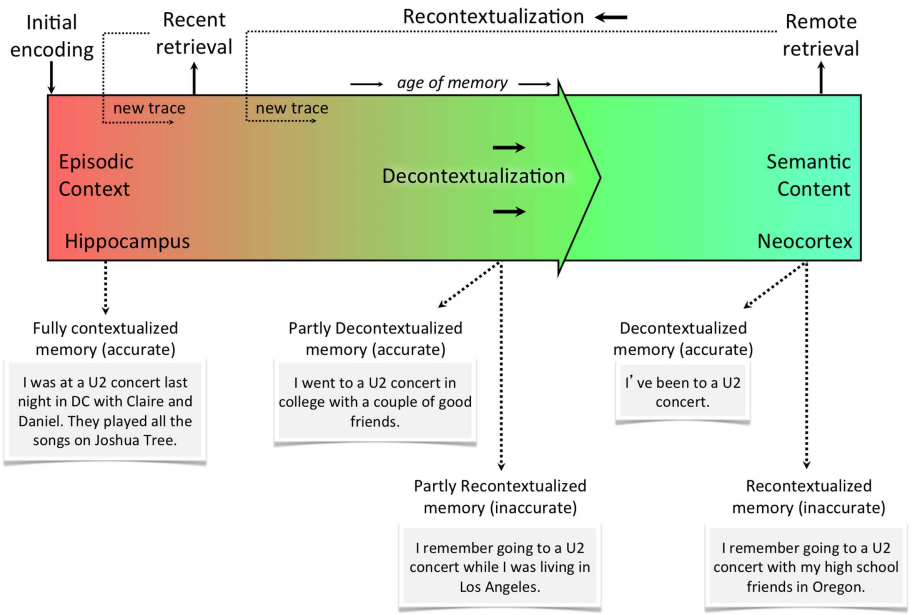


FIGURE 2 | The recontextualization continuum. Memories are most rich in episodic context the moment they are first encoded. With every subsequent reactivation (whether it's internally or externally cued), the memory becomes less episodic and more semantic (i.e., decontextualized). Every time a memory is retrieved, however, it can be recontextualized or re-encoded as a new trace with some overlapping features and some new ones. This means memories recalled from the distant past could either be decontextualized and accurate or recontextualized and inaccurate. Of course, neither accuracy or contextualization is a categorical assignment for the memory, but rather each memory can be described in terms of the accuracy of its details and the degree to which they are contextual (i.e., episodic).

strengthens some components of the memory and distorts others. The neocortex, at the very right of the continuum, is the final storage site of semantic memories that have been consolidated using slow cortical dynamics and trace interference over time. At the neocortical stage, recurrent and overlapping details have become relatively crystallized as the memory trace has been reconsolidated, but non-overlapping details are more transient and may be unique to a given recollective experience. That is, retrieval at any point in time results in a new trace that is stored as a slightly alternate version of the original memory. Retrieval at different points in this continuum is shown using examples. Altering contextual details may involve a large distortion (e.g., misremembering the city in which something occurred) or a very small one (e.g., misremembering which side of the sofa you were sitting on). Importantly, however, any deviation from the original representation is likely to correspond to a deviation from the initial neural representation of that memory trace. Even if a given retrieval event produces a memory trace that highly overlaps with the original memory, any amount of difference may be sufficient to induce competition.

Figure 3A is another demonstration of the change in contextual details over time that is predicted by CTT. Recent memories are high in accurate details, low in semantic content (which has not yet been consolidated), and low in inaccurate details, as the hippocampus has not yet had an opportunity to distort the memory owing to only a few replay/reactivation events. Remote memories, on the other hand, are low in accurate details, high in semantic content (which is now consolidated in the neocortex), and high in inaccurate details, as the hippocampus has had ample opportunity to distort the memory across numerous replay/reactivation events. The decline in accuracy of the memory follows the typical forgetting curve of Ebbinghaus (1885).

The increase in semantic strength is assumed to be monotonic and linear, although it is quite possible that it follows the same curvilinear pattern. Replay studies repeatedly demonstrate reactivation events in the short term (minutes, hours), with very few on the order of days (reviewed in Sutherland et al., 2010). Thus it is possible that most events leading to consolidation occur in the short term and the memory asymptotes quickly. However, in the absence of robust data for remote replay (exceeding several days), the exact pattern is difficult to infer. Importantly, CTT only makes assumptions about the slopes of these curves relative to one another and not about the exact shape of any particular curve.

To summarize, below are the central tenets of CTT:

1. Every time a memory is reactivated, the hippocampus recontextualizes the memory by re-encoding a similar but not identical memory trace that is stored using associative connectivity between the hippocampus and neocortex.
2. Memories are decontextualized over time by competitive interference among these similar but not identical multiple memory traces. This simultaneously leads to consolidation of semantic memory in the neocortex and loss of episodic details.
3. Veridical episodic details are only available in very recent memories. As memories get older, these details are replaced by recontextualized details stored by the hippocampus that give rise to illusory memories that become more prevalent as the

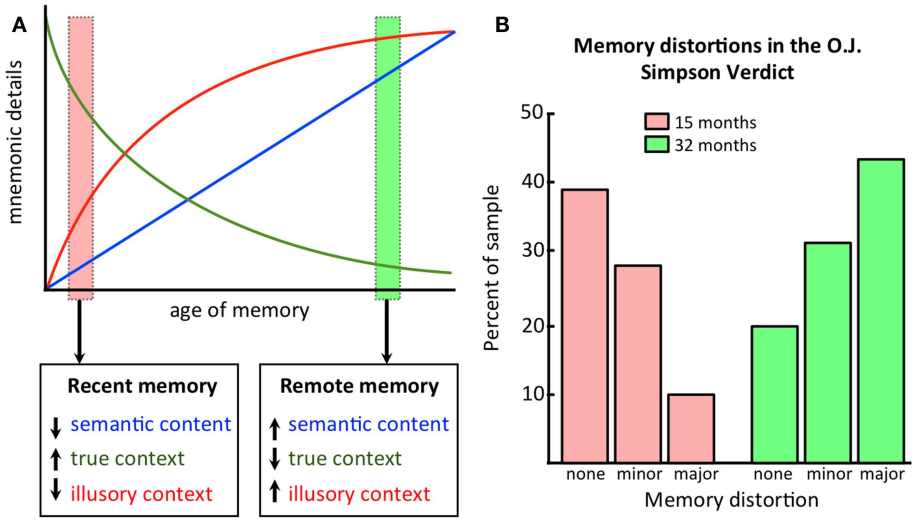


FIGURE 3 | Illusory details build up as memories get older. **(A)** A conceptual representation of how information content changes as a function of the age of the memory. Semantic content increases with consolidation, while true contextual details are replaced by illusory details; **(B)** An empirical demonstration of how illusory details increase as a function of time. See text for discussion. Data plotted based on values from Schmolck et al. (2000).

age of the memory increases. In other words, recent episodic and remote episodic memories vary in accuracy of details and strength of semantic content.

HARMONIZING CTT WITH PRE-EXISTING IDEAS

As we previously mentioned, CTT borrows elements from many existing theories and models. It is largely consistent with indexing theory (Teyler and DiScenna, 1986) and stresses the role of the hippocampus in encoding and binding the initial memory traces, and acting as an index during retrieval. Much like the CLS (McClelland et al., 1995) framework, CTT also assumes that the reactivation of hippocampal-neocortical traces strengthens the cortico-cortical traces leading to consolidation of memories. On the other hand, CTT also assumes that each reactivation of the memory results in a new trace and not just the reactivation of the old trace, which is consistent with MTT. Also consistent with the MTT proposal is the notion that the hippocampus is involved in the "reconstruction" rather than the "retrieval" of the memory. Nadel and Moscovitch (1998) also propose that reactivation of neocortical traces strengthens the links among multiple traces, which is the basis for building knowledge. This is further in agreement with CTT, however, we also suggest that the non-overlapping components of the traces compete with one another resulting in decontextualization in addition to consolidation.

We propose that the new hippocampal-neocortical traces formed are always partially but not completely overlapping with the original trace, resulting in competition for representation in the neocortex (this competition does not occur in the hippocampus due to pattern separation mechanisms discussed in detail below), leading to a selective strengthening of semantic information and weakening of contextual information. Thus, under CTT, the role of the hippocampus during retrieval is hypothesized to be the recontextualization of memories during retrieval to generate new competing traces. On the face of it, this may seem to be counterproductive at the level of the neocortex. As we will discuss below, we believe that this arises as a function of pattern separation computations necessary for episodic encoding. However, inducing competition may have a particular benefit in maintaining and retrieving memory traces. Namely, degradation of competing elements of a memory trace ensures that the important central features of that memory are not only preserved, but also strengthened.

The role of the hippocampus in recontextualization is also closely related to its role in mental imagery and imagining the future. Hassabis et al. (2007) demonstrated that this ability is impaired in hippocampal amnesic patients. They surmised that the hippocampus may contribute to the creation of new experiences by allowing disparate elements of prior memories to be bound in a spatial context. Addis and Schacter (2011) further extend this in a recent review of patient and neuroimaging findings to suggest that the hippocampus is also necessary for imagining the future and "episodic simulation." These roles in imagery are consistent with the notion of hippocampal recontextualization that we propose herein.

Our view is also largely consistent with the Distributed Reinstatement Theory of Sutherland et al. (2010) in which it is the frequency of replay/re-encoding episodes rather than the passage of time that leads to memories becoming independent of the hippocampus. Indeed, the central tenet of CTT is that reactivation events occurring as the age of the memory increases are the critical event in consolidation. While "age of memory" is plotted along the abscissa in the illustrations, it is used merely as a proxy that makes measurement feasible. Quantifying the number of reactivations, which is likely non-linear, is much less feasible. While one can pit these two alternatives (age of memory vs. number of reactivations) against each other in an experimental setup, only cued, not spontaneous, reactivation events can be assessed easily.

One potential possibility using advanced optogenetics techniques is to allow the hippocampus to engage in initial learning which could label the neurons involved using an immediate-early gene (e.g., Liu et al., 2012), then quantify reactivation events occurring within the labeled population only. Better yet, by silencing these neurons during specific time epochs, only circumscribed reactivations could be allowed. Thus, the effect of the passage of time vs. number of reactivations can be assessed directly.

The notion of competition for representation is not unique to memory by any means, and in fact seems to be a general principle of cortical operation. For example, it generally believed that in order for objects in the visual field to capture attention and be subjected to further neural processing they compete with one another for representation. Bottom-up and top-down influences can bias this competition by assigning priority to certain features or items but not others (Desimone and Duncan, 1995). A similar argument has been extended to the role of arousal in increasing the contrast between important and unimportant details in mnemonic representation (Mather and Sutherland, 2011). Thus, competition among memory *traces* (in contrast to competition among memory *systems*, which is widely accepted) is not an implausible idea, and in fact could be supported by very similar mechanisms to competition in other domains.

We further propose that the mechanisms involved in this competition arise as a result of hippocampal-neocortical dynamics and are particularly dependent on hippocampal processing. This harmonizes the model with the hippocampus's role in minimizing interference (i.e., pattern separation), a central tenet of the CLS. Below, we discuss this function in detail and suggest a potential mechanism by which it can facilitate cortical interference whilst minimizing hippocampal interference.

CONTRIBUTIONS OF PATTERN SEPARATION AND PATTERN COMPLETION

The hippocampus is capable of supporting rapid encoding of unique experiences by orthogonalizing incoming inputs such that interference is minimized, a function termed pattern separation, which is typically ascribed to the hippocampal dentate gyrus (DG) (Marr, 1971; Treves and Rolls, 1994; McClelland et al., 1995; O'Reilly and Norman, 2002; Norman and O'Reilly, 2003; Yassa and Stark, 2011). The hippocampus also has a well-recognized role in the formation of arbitrary associations using its recurrent collateral network in the CA3 subregion, a function termed pattern completion (Rolls, 2007). Recent evidence from animals (Nakazawa et al., 2003; Guzowski et al., 2004; Lee et al., 2004; Leutgeb et al., 2004, 2005, 2007; Vazdarjanova and Guzowski, 2004; Gold and Kesner, 2005; Kesner, 2007; McHugh et al., 2007) and humans (Bakker et al., 2008; Lacy et al., 2011) has provided strong support for the involvement of the hippocampus in these two important mnemonic computations. Though there is still some debate as to the precise nature of episodic memory, most in the field regard its core components as consisting of autobiographical details such as what occurred in addition to where and when. The capacity to orthogonalize overlapping input to create distinct memory traces, or to reinstate a particular memory trace based on partial or degraded input, are critical for encoding and remembering such details (Norman and O'Reilly, 2003; Norman, 2010). We suggest that pattern separation and pattern completion, provided they occur across different dimensions including space and time, are together necessary and sufficient to give rise to our episodic memory system with all of its richness, associativity, and flexibility (Yassa and Stark, 2011).

Given this deeper understanding of episodic memory mechanisms, it is important to discuss how the proposed CTT framework fits with these computations. First, let us make the case for pattern completion. This ability requires the reactivation of a previously stored representation when presented with a partial or a degraded cue. It is hypothesized to be a specific function of the CA3 region of the hippocampus due to recurrent collateral connectivity, which forms an autoassociative network and its innervation from the neocortex via the perforant path. This rapid retrieval is also balanced against new encoding in the CA3 region, which is subject to strong input by mossy fiber innervation from the DG granule cells (a pattern separation signal) (Treves and Rolls, 1994). Thus, the CA3 region regulates the dynamic balance between pattern separation and pattern completion at least in the spatial domain. A similar role may exist for the CA1 region in temporal pattern separation and completion, though there is less existing data on this phenomenon (see Hunsaker and Kesner, 2013 for a comprehensive recent review).

We suggest that pattern completion in the hippocampus reactivates the neocortical trace and leads to a strengthening of the overlapping trace over time. A pattern completion mechanism is necessary for CTT and could in theory underlie the ability to strengthen representations over time in a Hebbian fashion (using a slow cortical dynamic). The decay in non-overlapping features of the memory due to competitive interference is likewise presumed to occur in anti-Hebbian fashion.

Next, we turn to pattern separation. An important tenet of CTT is that every time a memory is reactivated, re-encoding of the trace occurs. This re-encoding contains some of the reactivated features (the attractor state), in addition to some unique associations that attempt to orthogonalize, though incompletely, the current representation from past memories. According to CTT, pattern separation in the hippocampus (in particular, the DG) is the most important factor in re-encoding a slightly different version of the experience (i.e. recontextualization), which causes the subsequent competition among overlapping traces in the neocortex. This can be viewed as a side effect of an otherwise very adaptive process, which acts to minimize interference in the initial storage of information, but *leads to competitive interference* in the cortex over time as previous memories are reactivated. This is a much more dynamic view of pattern separation and attempts to examine its long-term not just short term effects. It is important to note that this type of interference is unlike the catastrophic interference that would occur if sequential learning occurred too rapidly. Cortical interference is much slower and thus is much more stable in terms of network dynamics. Given the above, CTT is not only consistent with the pattern separation/completion framework but in fact relies on these computations to formulate its predictions.

HARMONIZING CTT WITH EXISTING DATA

Competitive trace theory is generally consistent with, and offers explanations for, much of the existing episodic memory literature

across species. While discussing every bit of evidence in the field is beyond the scope of this article, we present the case here using specific representative examples from behavioral studies of false memory and neuropsychological studies of amnesia in animals and humans.

BEHAVIORAL STUDIES OF FALSE MEMORY

To see the extent to which memory is non-veridical and is subject to constant updating, one need not look any further than the pioneering work of Bartlett (1932). Using the method of serial reproductions with material ranging from abstract drawings to stories such as "War of the Ghosts," Bartlett illustrated beautifully how memory can be altered every time it is retrieved. While this insightful work taught us about the impact of social bias on remembering, it also demonstrated unequivocally that memory is not veridical and is subject to constant change and reconstruction. Since Bartlett, research in false memory has enjoyed a rich tradition. Loftus (2005) has been investigating how humans adopt misinformation for over 30 years providing much of what we know about how false memories can be formed and how they can be extraordinarily rich in complexity and detail. False recall is also easily demonstrated by memory tasks such as the Deese–Roediger–McDermott (DRM) paradigm (Deese, 1959; Roediger and McDermott, 1995), and mnemonic discrimination tasks with similar lures (Yassa et al., 2011). Schacter discusses these memory "sins" as features of an adaptive memory system (Schacter, 1999). The frequency and abundance of these phenomena are consistent with the premise of recontextualization in CTT and suggest that reactivations lead to reconstructions of and updates to the initial memory.

Aside from the mere existence of false memory, for which there is extensive evidence within our field, CTT further proposes that the probability by which false memories are created are increased with repeated reactivations. Since reactivations are difficult to assess directly in humans unless they are induced using a cueing procedure, one can use the age of the memory as a proxy. We predict that the more time passing since initial encoding would be associated with increased tendency for false memories or distortions. In other words, the number of veridical details reported would decline with the age of the memory, while the number of illusory details would increase. There are many demonstrations of this effect, but we will discuss just two examples here.

The first example comes from a study by Schmolck et al. (2000) where college students were asked to recall the circumstances surrounding hearing about the verdict in the O. J. Simpson double murder trial after 3 days and were re-tested on their memories 15 or 32 months later. They found that as a function of a longer retention interval, the frequency of memory distortions increased (at 32 months, more than 40% of the recollections contained major distortions and only 29% were highly accurate). These results are shown in **Figure 3B**.

The second example comes from flashbulb memories. Brown and Kulik first described the flashbulb memory in 1977 as a vividly detailed memory of the circumstances surrounding an important emotional event, such as the assassination of John F. Kennedy (Brown and Kulik, 1977). Neisser (1982) wrote of his own flashbulb memory of the Japanese attack on Pearl Harbor on Sunday, December 7th, 1941. He recalled that he was listening to a baseball game on the radio. Many years later, it occurred to him that no baseball games are played in December (it was later suggested that it was actually a football game). It is now well accepted that although flashbulb memories are high in vividness, accuracy in many cases is low. A more recent study by Talarico and Rubin (2003) suggested that confidence in flashbulb memories increases while accuracy decreases over time. The investigators tested college students on their memory of first hearing about the September 11th terrorist attacks the day after the events occurred. Repeat testing occurred at 1, 6, or 32 weeks later. They found that the decline in accuracy for flashbulb memories was no different than everyday memories, however ratings of vividness and confidence did not decline for flashbulb memories. This report is also consistent with CTT's predictions, as the inclusion of fictitious details over time may give the illusion of accuracy and thus, recollection confidence (i.e., metamemory) remains high.

NEUROPSYCHOLOGICAL STUDIES OF HUMAN AMNESIA

While it is commonly agreed upon that cases of human amnesia suggest that remote retrograde memory is relatively intact, there is less agreement about whether the intact memories are rich enough in contextual detail to be deemed episodic or whether the recalled memories are more semantic in nature. SMSC asserts that those memories are truly episodic as they have become consolidated and become independent of the hippocampus long before hippocampal damage occurred. MTT, on the other hand, asserts that these memories are not entirely episodic because the hippocampus continues to be required for remote episodic memory recall.

As previously mentioned, Corkin characterized H. M.'s memories as "semanticized" or lacking in episodic detail, which is consistent with MTT. Other amnesia cases have demonstrated similar deficits in remote memories (Hirano and Noguchi, 1998; Moscovitch et al., 2000; Cipolotti et al., 2001). However, work by Squire and colleagues has strongly suggested that with more detailed neuropsychological investigations, the quality of retrieved remote memories in amnesia is similar to controls (Bayley et al., 2003; Kirwan et al., 2008). Squire and colleagues argue that the impairment in remote memory found in some cases of amnesia is secondary to non-MTL damage. In the absence of detailed neuroanatomical quantification, it is difficult to know whether this is truly the case. Another potential confound is the absence of corroboration to ensure the veracity of these memories (e.g., informant or diaries) in most if not all cases. Thus, it is not known whether the details retrieved are accurate or fictitious.

While the literature on remote memory in human amnesia is subject to much debate with respect to the episodic nature of such memories, CTT's predictions have much to do with the veracity of these memories. Similar to MTT, it hypothesizes that the hippocampus continues to be important for remote memories, but for entirely different reasons. During recall of remote memories, the hippocampus recontextualizes or updates the memory. In its absence, a strong personal semantic memory is available in the cortex and can be accessed directly. It is important to note here that MTT proposes that retrieval is dependent on the hippocampus because the hippocampus is required to reconstruct the memory of the episode within a spatial scaffold (Nadel and Moscovitch,

1998), thus a non-hippocampal memory would lack spatial context. CTT, on the other hand, proposes that any context (spatial or otherwise) can additionally be consolidated and strengthened to become independent of the hippocampus, as long as it is overlapping and not interfering with prior exposures. The critical difference between the two models is the explicit role assigned for overlap and interference in CTT.

Whether this personal semantic memory has associated contextual detail is not a categorical distinction but rather depends on the position of this memory on the contextualization continuum previously discussed. Thus, some memories may have more contextual details than others. The counterintuitive prediction of CTT here, however, is that amnesic patients will have remote memories that are more accurate than healthy controls, since the absence of a hippocampus prevents the recontextualization and reconstruction of those memories. While the data supporting this account are only circumstantial, autobiographical memory reports from patients like E. P. do suggest that autobiographical memories were less likely to be embellished or changed despite repeated recall in amnesia (Bayley et al., 2003).

Overall, the data from human amnesia cannot be used as strong support for CTT or any other model for recent vs. remote memory, given the disagreements about the (1) quality (e.g., richness, vividness, etc.) of the memories retrieved, (2) quantity of the memories retrieved, (3) accuracy of the memories retrieved, and (4) neuroanatomical characterization of medial temporal lobe damage. It is our hope, however, that the additional predictions afforded by CTT provide a platform for future studies with amnesic patients that may support or refute some of these basic ideas.

RODENT MODELS OF RETROGRADE AMNESIA

Most investigations of RA in the rodent hippocampus have been conducted using contextual fear conditioning. While several early examinations of recent vs. remote memories reported a temporal RA gradient (Kim and Fanselow, 1992; Maren et al., 1997; Anagnostaras et al., 1999), other studies have reported flat RA gradients (Lehmann et al., 2007; Sutherland et al., 2008). Investigations of RA in hippocampus lesioned rats in spatial navigation tasks have also reported generally flat RA gradients (Sutherland et al., 2001; Clark et al., 2005a,b; Martin et al., 2005). CTT predicts that the extent to which the hippocampus is critical for remote retrieval (i.e., whether there is a temporal or flat RA gradient) depends on (1) how much reactivation has occurred since the initial learning and (2) the nature of the retrieval task and whether it requires hippocampal recontextualization. The latter point is one deserving of further analysis. The ability of the hippocampus to engage in recontextualization should be a function of all of the other experiences it has encoded (these are the sources of interfering traces that can compete with the memory with each reactivation), thus factors such as rearing in rich vs. impoverished environments can significantly influence the results.

This is evidenced by phenomena such as immediate shock deficit (ISD: Fanselow, 1986) and the context pre-exposure effect (Fanselow, 1990), where a critical role of the hippocampus in learning about the environment in contextual fear conditioning is demonstrated. It is likely that the parameters of these phenomena (e.g., latency required for ISD or pre-exposure) are dependent on the animal's prior history. Most studies with rodents use individually housed rats in impoverished conditions, which results in the hippocampus operating under suboptimal conditions. We suggest that the hippocampus' ability to facilitate cortical interference by encoding recontextualized versions of the memories will depend on this prior history. In light of this, a re-examination of lesion studies in rodents and future studies using animals reared in enriched environments are required to fully test the predictions of CTT.

Several studies have shown that hippocampal learning can compete with learning in non-hippocampal systems (Maren et al., 1997; Frankland et al., 1998; Driscoll et al., 2005; Lehmann et al., 2006; Sutherland et al., 2006; Wiltgen et al., 2006), suggesting that different memory traces do compete for representational resources in the brain. In a recent demonstration, Sutherland and colleagues (Sparks et al., 2011) showed that a non-hippocampally acquired contextual fear memory (learned while hippocampus was temporarily inactivated) was susceptible to interference or competition from the hippocampus when it was subsequently reactivated. These findings are directly predicted by CTT and further demonstrate the impact of competition among hippocampal-neocortical memory traces. These data also offer an alternative account to demonstrations of anterograde amnesia following pre-training hippocampal inactivation (e.g., Bast et al., 2001). While it is possible that the inactivation prevented the animals from learning the task, another possibility is that the reactivation of the hippocampus after learning disrupted performance on test due to competition with memory traces formed outside the hippocampus.

The above data suggest that there is indeed interference and competition between hippocampal and neocortical memories. The CTT formalizes this competition and describes a potential mechanism (via hippocampal pattern separation) by which it can occur.

MEMORY UPDATING AND RECONSOLIDATION

It has been long known that retrieved memories are labile and can be disrupted. For example, Donald Lewis's seminal experiments in 1968 demonstrated that reactivated memories can be disrupted by electroconvulsive shock (Misanin et al., 1968). Based on this work, Lewis proposed that reactivating a memory brings it into an active state that is vulnerable to disruption by external agents (Lewis, 1979). In 2000, Nader et al. (2000a) demonstrated that a protein synthesis inhibitor (anisomycin) resulted in the disruption of a reactivated fear memory. The authors proposed a mechanism for this disruption they termed "reconsolidation," which essentially posits that reactivation results into two distinct events: an unbinding of the synapses representing the memory and a concurrent second round of protein synthesis to re-instantiate the memory. Protein synthesis inhibitors, they surmised, blocked the second event, thus disrupting the memory permanently (Nader et al., 2000b). Although initial reports were inconsistent across laboratories [e.g., memory loss was not always permanent (see Power et al., 2006)] and the widespread effects of protein synthesis inhibitors were seen as potential confounds (Rudy et al., 2006), more recent data has partly supported the notion that reconsolidation may

occur under some conditions and may be at least one way in which memory updating can occur (Besnard et al., 2012).

Conceptually, CTT is consistent with both Lewis's *Active Trace Theory* and reconsolidation theory in that it puts great emphasis on memory reactivation as the critical event by which a memory can be updated. We also similarly suggest that intervening with the memory trace during retrieval can disrupt it. However, the exact mechanisms diverge. CTT's account is based on interference among competing memory traces and not a synaptic "resetting" *per se*. The extent to which spontaneous recovery can be observed (as in extinction procedures) will depend on the extent of the interference among the competing traces. If the competition results in suppression of much of the original memory, spontaneous recovery may not be observed.

More directly relevant to CTT, Monfils et al. (2009) recently suggested that preceding an extinction procedure with a single reactivation trial can disrupt fear memory. The same procedure has recently been applied to disrupt fear memories in humans (Schiller et al., 2010) and decrease cue-induced craving in human heroin users (Xue et al., 2012). While the results of this type of memory disruption have been interpreted in terms of reconsolidation, they do not necessarily speak to the underlying mechanism. We argue that results from retrieval-extinction procedures are more consistent with the CTT account, where retrieval is associated with a re-encoding of the memory, which only partially overlaps with the original memory and can compete with it for storage. In the retrieval-extinction procedure this process is greatly accelerated by providing the competing memory directly in the extinction trials.

It is likely that this update process happens all the time, however, there is typically no systematic attempt to extinguish behavior with competing memories in every day circumstances. This results in a subtle update that removes some features of the memory and adds others. In an experimental setting, however, where a competing memory is explicitly encoded to extinguish the fear behavior, it is much easier to observe a complete or near-complete ablation of the memory. Episodic memories in humans are also likely much richer than fear memories in animals thus a complete ablation would be more difficult to instantiate as the competition needs to occur repeatedly and over an extended period of time.

MAKING NEW PREDICTIONS BASED ON CTT

The CTT framework represents a plausible mechanism by which hippocampal-neocortical traces are established and updated. It makes a set of empirical predictions that can be tested directly in animals or humans. We highlight some of these predictions here, in hopes that they will be instigate such research in the future to attempt to support or refute CTT's core premises.

- The first prediction is the remote episodic memories should be less accurate than recent episodic memories. We discussed some evidence for this in studies of false memory as well as human amnesia, however the prediction needs to be tested more directly using veridical records of information. This prediction may also be tested using an animal model where the accuracy of the memory can be tested using a discrimination/generalization procedure. For example, Wiltgen and Silva (2007) provide supporting evidence for this by demonstrating that context generalization increases as a function of time, consistent with our proposal that more remote memories are less context-specific.
- The second prediction is that amnesia patients as well as rodents with hippocampal lesions should have more accurate remote semantic memories compared to healthy controls. This follows from the premise that having a hippocampus has the capacity to distort the memory every time it is recalled. Removing this brain region should also remove the capacity for distortion, leaving an intact semantic memory without associated illusory details.
- The third prediction is that whether a flat or graded RA curve is observed in rodent studies will depend on whether contextual information was repeatedly presented to the animal. If contextual information was presented more than once, some amount of this context will become semanticized, and thus hippocampal damage will lead to a flat RA gradient. However, if contextual information was presented only once, there isn't an opportunity for semantic information to build up, and hippocampus damage will lead to a graded RA. Controlled experiments with amnesic patients or lesioned animals can test this prediction. It is interesting to note here that flat or graded RA curves can be obtained also with cortical lesions. Cho and Kesner (1996) showed that a flat RA gradient could be obtained with parietal cortical lesions while a temporally graded RA could be obtained with entorhinal cortical lesions in a spatial discrimination task. Thus, the location of the lesion, as well as the degree of contextual repetition are both hypothesized to influence the temporal gradient of RA.
- The fourth prediction is that the fidelity of mnemonic representations should change with repeated reactivations in the hippocampus and the neocortex. The degree of overlap in representations from exposure to exposure should predict how strong the memory is in a subsequent test (i.e., should generate a generalizable representation), while the degree of stochasticity should predict how contextual the memory is. Furthermore, given the hippocampus' powerful capacity for orthogonalizing inputs, it may be the case that repetitions of identical study items may nonetheless induce competition as a result of varying external and internal contextual elements. This prediction can be tested using multivariate pattern classification techniques such as representational similarity analyses (Kriegeskorte et al., 2008) applied to fMRI or neurophysiological recording data.
- The fifth prediction is that there will be evidence for interference in the neocortex and not just the hippocampus, however, the timescale for neocortical trace interference will be much slower than the hippocampus and the mechanism will be more dependent on competitive inhibition via LTD-like mechanisms rather than pattern separation. This prediction may prove especially difficult to assess, though neurophysiological recordings and gene expression assays in animal models, or post-exposure representational similarity analyses via fMRI in humans may provide some insight. It is important to note here that LTD mechanisms are not hypothesized to be limited to the neocortex or to competitive inhibition *per se*. There is strong evidence that these mechanisms are also necessary for the acquisition of new memories in the hippocampus (Kemp and Manahan-Vaughan, 2004). Thus, this is likely a much more general mechanism, which could serve several purposes for our memory system.

CONCLUSION

The role of the hippocampus in retrieval has been subject to much debate. The two schools of thought on the topic, SMSC and MTT, have had divergent predictions and so far, it is still not clear which model best describes the empirical data. We propose an alternative model in the form of a continuum and hypothesize that the role of the hippocampus during retrieval is recontextualization of memories along this continuum. This process, in turn, facilitates competition and trace interference in the cortex such that that consolidated memory traces become semantic. Our model explains much of the current data and provides fodder for future research in the form of testable empirical predictions. It may prove helpful as we shift our focus from categorical assignments such as "episodic" and move toward a more computationally grounded, cross-species compatible, continuum approach to declarative memory.

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REFERENCES

Addis, D. R., and Schacter, D. L. (2011). The hippocampus and imagining the future: where do we stand? *Front. Hum. Neurosci.* 5:173. doi:10.3389/fnhum.2011.00173

Anagnostaras, S. G., Maren, S., and Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *J. Neurosci.* 19, 1106–1114.

Bakker, A., Kirwan, C. B., Miller, M., and Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science* 319, 1640–1642. doi:10.1126/science.1152882

Bartlett, F. F. C. (1932). *Remembering: A Study in Experimental and Social Psychology*. Cambridge: Cambridge University Press.

Bast, T., Zhang, W.-N., and Feldon, J. (2001). The ventral hippocampus and fear conditioning in rats. *Exp. Brain Res.* 139, 39–52. doi:10.1007/s002210100746

Bayley, P. J., Hopkins, R. O., and Squire, L. R. (2003). Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron* 38, 135–144. doi:10.1016/S0896-6273(03)00156-9

Besnard, A., Caboche, J., and Laroche, S. (2012). Reconsolidation of memory: a decade of debate. *Prog. Neurobiol.* 99, 61–80. doi:10.1016/j.pneurobio.2012.07.002

Brown, R., and Kulik, J. (1977). Flashbulb memories. *Cognition* 5, 73–99. doi:10.1016/0010-0277(77)90018-X

Buckner, R. L., Wheeler, M. E., and Sheridan, M. A. (2001). Encoding processes during retrieval tasks. *J. Cogn. Neurosci.* 13, 406–415. doi:10.1162/08989290151137430

Cho, Y. H., and Kesner, R. P. (1996). Involvement of entorhinal cortex or parietal cortex in long-term spatial discrimination memory in rats: retrograde amnesia. *Behav. Neurosci.* 110, 436–442. doi:10.1037/0735-7044.110.3.436

Cipolotti, L., Shallice, T., Chan, D., Fox, N., Scahill, R., Harrison, G., et al. (2001). Long-term retrograde amnesia ... the crucial role of the hippocampus. *Neuropsychologia* 39, 151–172. doi:10.1016/S0028-3932(00)00103-2

Clark, R. E., Broadbent, N. J., and Squire, L. R. (2005a). Hippocampus and remote spatial memory in rats. *Hippocampus* 15, 260–272. doi:10.1002/hipo.20056

Clark, R. E., Broadbent, N. J., and Squire, L. R. (2005b). Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus* 15, 340–346. doi:10.1002/hipo.20076

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nat. Rev. Neurosci.* 3, 153–160. doi:10.1038/nrn726

Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J. Neurophysiol.* 96, 1902–1911. doi:10.1152/jn.01029.2005

Deese, J. (1959). On the prediction of occurrence of particular verbal intrusions in immediate recall. *J. Exp. Psychol.* 58, 17–22. doi:10.1037/h0046671

Desimone, R., and Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* 18, 193–222. doi:10.1146/annurev.ne.18.030195.001205

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn. Sci. (Regul. Ed.)* 11, 379–386. doi:10.1016/j.tics.2007.08.001

Driscoll, I., Howard, S. R., Prusky, G. T., Rudy, J. W., and Sutherland, R. J. (2005). Seahorse wins all races: hippocampus participates in both linear and non-linear visual discrimination learning. *Behav. Brain Res.* 164, 29–35. doi:10.1016/j.bbr.2005.05.006

Ebbinghaus, H. (1885). *Memory. A Contribution to Experimental Psychology (Translated to English in 1913)*. New York: Teachers College, Columbia University.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., and Engel, S. A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nat. Neurosci.* 3, 1149–1152. doi:10.1038/80671

Fanselow, M. S. (1986). Associative vs. topographical accounts of the immediate shock-freezing deficit in rats: implications for the response selection rules governing species-specific defensive reactions. *Learn. Motiv.* 17, 16–39. doi:10.1016/0023-9690(86)90018-4

Fanselow, M. S. (1990). Factors governing one-trial contextual conditioning. *Anim. Learn. Behav.* 18, 264–270. doi:10.3758/BF03205285

Frankland, P. W., and Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130. doi:10.1038/nrn1607

Frankland, P. W., Cestari, V., Filipkowski, R. K., McDonald, R. J., and Silva, A. J. (1998). The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. *Behav. Neurosci.* 112, 863–874. doi:10.1037/0735-7044.112.4.863

Gallo, D. A., Roediger, H. L., and McDermott, K. B. (2001). Associative false recognition occurs without strategic criterion shifts. *Psychon. Bull. Rev.* 8, 579–586.

Gold, A. E., and Kesner, R. P. (2005). The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. *Hippocampus* 15, 808–814. doi:10.1002/hipo.20103

Goshen, I., Brodsky, M., Prakash, R., Wallace, J., Gradinaru, V., Ramakrishnan, C., et al. (2011). Dynamics of Retrieval Strategies for Remote Memories. *Cell* 147, 678–689. doi:10.1016/j.cell.2011.09.033

Guzowski, J. F., Knierim, J. J., and Moser, E. I. (2004). Ensemble dynamics of hippocampal regions CA3 and CA1. *Neuron* 44, 581–584. doi:10.1016/j.neuron.2004.11.003

Haist, F., Bowden Gore, J., and Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nat. Neurosci.* 4, 1139–1145. doi:10.1038/nn739

Hassabis, D., Kumaran, D., Vann, S. D., and Maguire, E. A. (2007). Patients with hippocampal amnesia cannot imagine new experiences. *Proc. Natl. Acad. Sci. U.S.A.* 104, 1726–1731. doi:10.1073/pnas.0610561104

Hirano, M., and Noguchi, K. (1998). Dissociation between specific personal episodes and other aspects of remote memory in a patient with hippocampal amnesia. *Percept. Mot. Skills* 87, 99–107. doi:10.2466/pms.1998.87.1.99

Holdstock, J. S., Mayes, A. R., Gong, Q. Y., Roberts, N., and Kapur, N. (2004). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus* 15, 203–215. doi:10.1002/hipo.20046

Hunsaker, M. R., and Kesner, R. P. (2013). The operation of pattern separation and pattern completion processes associated with different attributes or domains of memory. *Neurosci. Biobehav. Rev.* 37, 36–58. doi:10.1016/j.neubiorev.2012.09.014

Kemp, A., and Manahan-Vaughan, D. (2004). Hippocampal long-term depression and long-term potentiation encode different aspects of novelty acquisition. *Proc. Natl. Acad. Sci. U.S.A.* 101, 8192–8197. doi:10.1073/pnas.0402650101

Kensinger, E. A., and Schacter, D. L. (2007). Remembering the specific visual details of presented objects: neuroimaging evidence for effects of emotion. *Neuropsychologia* 45, 2951–2962. doi:10.1016/j.neuropsychologia.2007.05.024

Kesner, R. P. (2007). Behavioral functions of the CA3 subregion of the hippocampus. *Learn. Mem.* 14, 771–781.

Kim, J., and Yassa, M. A. (2013). Assessing recollection and familiarity of similar lures in a behavioral pattern separation task. *Hippocampus* 23, 287–294. doi:10.1002/hipo.22087

Kim, J. J., and Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science* 256, 675–677. doi:10.1126/science.1585183

Kirwan, C. B., Bayley, P. J., Galván, V. V., and Squire, L. R. (2008). Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. *Proc. Natl. Acad. Sci. U.S.A.* 105, 2676–2680. doi:10.1073/pnas.0712155105

Kriegeskorte, N., Mur, M., and Bandettini, P. (2008). Representational similarity analysis – connecting the branches of systems neuroscience. *Front. Syst. Neurosci.* 2:4. doi:10.3389/neuro.06.004.2008

Lacy, J. W., Yassa, M. A., Stark, S. M., Muftuler, L. T., and Stark, C. E. L. (2011). Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. *Learn. Mem.* 18, 15–18. doi:10.1101/lm.1971111

Lee, I., Yoganarasimha, D., Rao, G., and Knierim, J. J. (2004). Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. *Nature* 430, 456–459. doi:10.1038/nature02739

Lehmann, H., Lacanilao, S., and Sutherland, R. J. (2007). Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *Eur. J. Neurosci.* 25, 1278–1286. doi:10.1111/j.1460-9568.2007.05374.x

Lehmann, H., Lecluse, V., Houle, A., and Mumby, D. G. (2006). Retrograde amnesia following hippocampal lesions in the shock-probe conditioning test. *Hippocampus* 16, 379–387. doi:10.1002/hipo.20159

Leutgeb, J. K., Leutgeb, S., Moser, M.-B., and Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science* 315, 961–966. doi:10.1126/science.1135801

Leutgeb, J. K., Leutgeb, S., Treves, A., Meyer, R., Barnes, C. A., McNaughton, B. L., et al. (2005). Progressive transformation of hippocampal neuronal representations in "morphed" environments. *Neuron* 48, 345–358. doi:10.1016/j.neuron.2005.09.007

Leutgeb, S., Leutgeb, J. K., Treves, A., Moser, M.-B., and Moser, E. I. (2004). Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science* 305, 1295–1298. doi:10.1126/science.1100265

Lewis, D. J. (1979). Psychobiology of active and inactive memory. *Psychol. Bull.* 86, 1054–1083. doi:10.1037/0033-2909.86.5.1054

Liu, X., Ramirez, S., Pang, P. T., Puryear, C. B., Govindarajan, A., Deisseroth, K., et al. (2012). Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484, 381–385. doi:10.1038/nature11028

Loftus, E. F. (2005). Planting misinformation in the human mind: a 30-year investigation of the malleability of memory. *Learn. Mem.* 12, 361–366.

Maren, S., Aharonov, G., and Fanselow, M. S. (1997). Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav. Brain Res.* 88, 261–274. doi:10.1016/S0166-4328(97)00088-0

Marr, D. (1971). Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 262, 23–81. doi:10.1098/rstb.1971.0078

Martin, S. J., De Hoz, L., and Morris, R. G. M. (2005). Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia* 43, 609–624. doi:10.1016/j.neuropsychologia.2004.07.007

Mather, M., and Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.* 6, 114–133. doi:10.1177/1745691611400234

McClelland, J. L., McNaughton, B. L., and O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457. doi:10.1037/0033-295X.102.3.419

McHugh, T. J., Jones, M. W., Quinn, J. J., Balthasar, N., Coppari, R., Elmquist, J. K., et al. (2007). Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science* 317, 94–99. doi:10.1126/science.1140263

Milner, B., Squire, L. R., and Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron* 20, 445–468. doi:10.1016/S0896-6273(00)80987-3

Misanin, J. R., Miller, R. R., and Lewis, D. J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* 160, 554–555. doi:10.1126/science.160.3827.554

Monfils, M.-H., Cowansage, K. K., Klann, E., and LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science* 324, 951–955. doi:10.1126/science.1167975

Moscovitch, M., Yaschyshyn, T., Ziegler, M., and Nadel, L. (2000). "Remote episodic memory and retrograde amnesia: was Endel Tulving right all along?," in *Memory, Consciousness and the Brain: The Tallinn Conference*, ed. E. Tulving (Philadelphia, PA: Psychology Press/Taylor & Francis), 331–345.

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* 7, 217–227. doi:10.1016/S0959-4388(97)80010-4

Nadel, L., and Moscovitch, M. (1998). Hippocampal contributions to cortical plasticity. *Neuropharmacology* 37, 431–439. doi:10.1016/S0028-3908(98)00057-4

Nader, K., Schafe, G. E., and Le Doux, J. E. (2000a). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406, 722–726. doi:10.1038/35021052

Nader, K., Schafe, G. E., and LeDoux, J. E. (2000b). The labile nature of consolidation theory. *Nat. Rev. Neurosci.* 1, 216–219. doi:10.1038/35044580

Nakazawa, K., Sun, L. D., Quirk, M. C., Rondi-Reig, L., Wilson, M. A., and Tonegawa, S. (2003). Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. *Neuron* 38, 305–315. doi:10.1016/S0896-6273(03)00165-X

Neisser, U. (1982). "Snapshots or benchmarks?," in *Memory Observed*, ed. U. Neisser (New York: W. H. Freeman), 45.

Norman, K. A. (2010). How hippocampus and cortex contribute to recognition memory: revisiting the complementary learning systems model. *Hippocampus* 20, 1217–1227. doi:10.1002/hipo.20855

Norman, K. A., and O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychol. Rev.* 110, 611–646. doi:10.1037/0033-295X.110.4.611

O'Reilly, R. C., and Norman, K. A. (2002). Hippocampal and neocortical contributions to memory: advances in the complementary learning systems framework. *Trends Cogn. Sci. (Regul. Ed.)* 6, 505–510. doi:10.1016/S1364-6613(02)02005-3

Power, A. E., Berlau, D. J., McGaugh, J. L., and Steward, O. (2006). Anisomycin infused into the hippocampus fails to block "reconsolidation" but impairs extinction: the role of re-exposure duration. *Learn. Mem.* 13, 27–34.

Roediger, H. L., and McDermott, K. B. (1995). Creating false memories: remembering words not presented in lists. *J. Exp. Psychol. Learn. Mem. Cogn.* 24, 803–814. doi:10.1037/0278-7393.21.4.803

Roediger, H. L., McDermott, K. B., Pisoni, D. B., and Gallo, D. A. (2004). Illusory recollection of voices. *Memory* 12, 586–602. doi:10.1080/09658210344000125

Rolls, E. T. (2007). An attractor network in the hippocampus: theory and neurophysiology. *Learn. Mem.* 14, 714–731.

Rudy, J. W., Biedenkapp, J. C., Moineau, J., and Bolding, K. (2006). Anisomycin and the reconsolidation hypothesis. *Learn. Mem.* 13, 1–3.

Ryan, L., Nadel, L., Keil, K., Putnam, K., Schnyer, D., Trouard, T., et al. (2001). Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus* 11, 707–714. doi:10.1002/hipo.1086

Schacter, D. L. (1999). The seven sins of memory. Insights from psychology and cognitive neuroscience. *Am. Psychol.* 54, 182–203. doi:10.1037/0003-066X.54.3.182

Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., Ledoux, J. E., and Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 463, 49–53. doi:10.1038/nature08637

Schmolck, H., Buffalo, E. A., and Squire, L. R. (2000). Memory distortions develop over time: recollections of the O.J. Simpson trial verdict after 15 and 32 months. *Psychol. Sci.* 11, 39–45. doi:10.1111/1467-9280.00212

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatr.* 20, 11–21. doi:10.1136/jnnp.20.1.11

Sherry, D. F., and Schacter, D. L. (1987). The evolution of multiple memory systems. *Psychol. Rev.* 94, 439–454. doi:10.1037/0033-295X.94.4.439

Sparks, F. T., Lehmann, H., and Sutherland, R. J. (2011). Between-systems memory interference during retrieval. *Eur. J. Neurosci.* 34, 780–786. doi:10.1111/j.1460-9568.2011.07796.x

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron* 61, 6–9. doi:10.1016/j.neuron.2008.12.023

Squire, L. R., and Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177. doi:10.1016/0959-4388(95)80023-9

Squire, L. R., Cohen, N. J., and Zouzounis, J. A. (1984). Preserved memory in retrograde amnesia: sparing of a recently acquired skill. *Neuropsychologia* 22, 145–152. doi:10.1016/0028-3932(84)90057-5

Stahl, C., and Klauer, K. C. (2008). A simplified conjoint recognition paradigm for the measurement of gist and verbatim memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 34, 570–586. doi:10.1037/0278-7393.34.3.570

Stark, C. E., and Okado, Y. (2003). Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *J. Neurosci.* 23, 6748–6753.

Stefanacci, L., Buffalo, E. A., Schmolck, H., and Squire, L. R. (2000). Profound amnesia after damage to the medial temporal lobe: a neuroanatomical and neuropsychological profile of patient E. P. *J. Neurosci.* 20, 7024–7036.

Suddendorf, T., and Corballis, M. C. (1997). Mental time travel and the evolution of the human mind. *Genet. Soc. Gen. Psychol. Monogr.* 123, 133–167.

Sutherland, R. J., Lehmann, H., Spanswick, S. C., Sparks, F. T., and Melvin, N. R. (2006). Growth Points in Research on Memory and Hippocampus. *Can. J. Exp. Psychol.* 60, 166–174. doi:10.1037/cjep20060016

Sutherland, R. J., O'Brien, J., and Lehmann, H. (2008). Absence of systems consolidation of fear memories after dorsal, ventral, or complete hippocampal damage. *Hippocampus* 18, 710–718. doi:10.1002/hipo.20431

Sutherland, R. J., Sparks, F. T., and Lehmann, H. (2010). Hippocampus and retrograde amnesia in the rat model: a modest proposal for the situation of systems consolidation. *Neuropsychologia* 48, 2357–2369. doi:10.1016/j.neuropsychologia.2010.04.015

Sutherland, R. J., Weisend, M. P., Mumby, D., Astur, R. S., Hanlon, F. M., Koerner, A., et al. (2001). Retrograde amnesia after hippocampal damage: recent vs. remote memories in two tasks. *Hippocampus* 11, 27–42. doi:10.1002/1098-1063(2001)11:1<27::AID-HIPO1017>3.0.CO;2-4

Talarico, J. M., and Rubin, D. C. (2003). Confidence, not consistency, characterizes flashbulb memories. *Psychol. Sci.* 14, 455–461. doi:10.1111/1467-9280.02453

Teyler, T. J., and DiScenna, P. (1985). The role of hippocampus in memory: a hypothesis. *Neurosci. Biobehav. Rev.* 9, 377–389.

Teyler, T. J., and DiScenna, P. (1986). The hippocampal memory indexing theory. *Behav. Neurosci.* 100, 147–154. doi:10.1037/0735-7044.100.2.147

Teyler, T. J., and Rudy, J. W. (2007). The hippocampal indexing theory and episodic memory: updating the index. *Hippocampus* 1169, 1158–1169. doi:10.1002/hipo.20350

Treves, A., and Rolls, E. T. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus* 4, 374–391. doi:10.1002/hipo.450040319

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204. doi:10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.3.CO;2-J

Vazdarjanova, A., and Guzowski, J. F. (2004). Differences in hippocampal neuronal population responses to modifications of an environmental context: evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. *J. Neurosci.* 24, 6489–6496. doi:10.1523/JNEUROSCI.0350-04.2004

Wiltgen, B. J., Sanders, M. J., Anagnostaras, S. G., Sage, J. R., and Fanselow, M. S. (2006). Context fear learning in the absence of the hippocampus. *J. Neurosci.* 26, 5484–5491. doi:10.1523/JNEUROSCI.2685-05.2006

Wiltgen, B. J., and Silva, A. J. (2007). Memory for context becomes less specific with time. *Learn. Mem.* 14, 313–317.

Wiltgen, B. J., Zhou, M., Cai, Y., Balaji, J., Karlsson, M. G., Parivash, S. N., et al. (2010). The hippocampus plays a selective role in the retrieval of detailed contextual memories. *Curr. Biol.* 20, 1336–1344. doi:10.1016/j.cub.2010.06.068

Xue, Y.-X., Luo, Y.-X., Wu, P., Shi, H.-S., Xue, L.-F., Chen, C., et al. (2012). A memory retrieval-extinction procedure to prevent drug craving and relapse. *Science* 336, 241–245. doi:10.1126/science.1215070

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., and Stark, C. E. L. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus* 21, 968–979. doi:10.1002/hipo.20808

Yassa, M. A., and Stark, C. E. L. (2011). Pattern separation in the hippocampus. *Trends Neurosci.* 34, 515–525. doi:10.1016/j.tins.2011.06.006

Yonelinas, A. P., Kroll, N. E. A., Quamme, J. R., Lazzara, M. M., Sauvé, M.-J., Widaman, K. F., et al. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nat. Neurosci.* 5, 1236–1241. doi:10.1038/nn961

Yonelinas, A. P., Otten, L. J., Shaw, K. N., and Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *J. Neurosci.* 25, 3002–3008. doi:10.1523/JNEUROSCI.5295-04.2005

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Context prediction analysis and episodic memory

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Events that happen at a particular place and time come to define our episodic memories. Extensive experimental and clinical research illustrate that the hippocampus is central to the processing of episodic memories, and this is in large part due to its analysis of context information according to spatial and temporal references. In this way, hippocampus defines ones expectations for a given context as well as detects errors in predicted contextual features. The detection of context prediction errors is hypothesized to distinguished events into meaningful epochs that come to be recalled as separate episodic memories. The nature of the spatial and temporal context information processed by hippocampus is described, as is a hypothesis that the apparently self-regulatory nature of hippocampal context processing may ultimately be mediated by natural homeostatic operations and plasticity. Context prediction errors by hippocampus are suggested to be valued by the midbrain dopamine system, the output of which is ultimately fed back to hippocampus to update memory-driven context expectations for future events. Thus, multiple network functions (both within and outside hippocampus) combine to result in adaptive episodic memories.

Keywords: hippocampus, prediction errors, prefrontal cortex, dopamine, striatum, memory, decision making

INTRODUCTION

Events are typically defined by the situations that are associated with significant outcomes. Each situation, or context, is multifaceted in that it includes not only the external sensory environment, but also our intrinsic motivational and emotional state, as well as social considerations. Thus it should not be surprising that the cells of the hippocampus, long thought to mediate episodic or event-based memories (e.g., O'Keefe and Nadel, 1978; Tulving, 2002), have been found to represent a variety of context-defining information. The challenge has been, however, to understand how these hippocampal representations of context-specific information are used to generate episodic memories. The following discusses the view that hippocampus represents context information in order to determine whether the expected contextual features match those currently being experienced. The identification of mismatches (termed *context prediction errors*) may lead to a cascading series of assessments through connected brain regions that could ultimately alter future decisions and update memories.

SPATIAL CONTEXT-DEPENDENCY OF HIPPOCAMPAL NEURAL CODES

It is generally accepted that hippocampus processes contextual information (e.g., Hirsh, 1974; Myers and Gluck, 1994; Anagnostaras et al., 2001; Maren, 2001; Fanselow and Poulos, 2005; Bouton et al., 2006). There are numerous demonstrations in which conditioned responses to contextual stimuli are eliminated with hippocampal damage while responses to discrete conditioned stimuli are unaffected (e.g., Kim and Fanselow, 1992; Phillips and LeDoux, 1992, 1994). Also, animals with hippocampal or entorhinal cortical damage do not show the normal decrement in conditioned responding after a shift in context (Penick and Solomon, 1991; Freeman et al., 1996a,b). The hippocampus of freely behaving animals is predisposed to represent context information within a spatial framework: during unrestrained navigation, hippocampal neurons fire selectively as animals traverse restricted areas of their environment, referred to as *place fields* (O'Keefe and Dostrovsky, 1971). As decades of research have shown (summarized in Mizumori, 2008), place fields are dynamic and integrated representations of multiple types of context-defining information. For example, changing any modality of cues, the motivational state, or the behaviors needed to perform the task result in alterations of place field properties, a process commonly referred to as *remapping*.

The readiness of place fields to remap is evident when changes are made to the visual environment (e.g., Ranck, 1973; O'Keefe, 1976; Olton et al., 1978; Muller and Kubie, 1987), such as its geometric features (e.g., Gothard et al., 1996; O'Keefe and Burgess, 1996; Wiener, 1996). Other sensory inputs also bias place field activity, including olfactory (Save et al., 2000), auditory (O'Keefe and Conway, 1978; McEchron and Disterhoft, 1999), and somatosensory information (Young et al., 1994). Thus, an extensive literature (Mizumori, 2008) verifies that hippocampal pyramidal neurons process multimodal sensory input. Hippocampal place fields are also sensitive to changes in a task's reward structure (Smith and Mizumori, 2006b; Wikenheiser and Redish, 2011). Smith and Mizumori (2006b) explicitly tested this idea by training rats to distinguish Context A from Context B according to where reward was expected to be found. The motivational, sensory, and behavioral requirements of task performance were purposely held constant across the two contexts so that changes in place fields could be attributed to the recall of a different memory. Place fields remapped at the beginning of trials in Context B, a time when there is heightened uncertainty about the context conditions. In a similar experiment, Wikenheiser and Redish

(2011) demonstrated that changes in reward contingency can modulate the trial-to-trial variability of hippocampal place cell activity, again suggesting that uncertainty can drive place field remapping. Finally, the relative contributions of sensory, motivation (including reward), or response information to a given place field vary with task demands, and this is evidenced by findings across many laboratories that place fields change when rats use identical information to solve tasks according to different mnemonic strategies (e.g., Ferbinteanu and Shapiro, 2003; Mizumori et al., 2004; Eschenko and Mizumori, 2007).

In sum, it is clear that place fields can come to represent different types of sensory, behavioral, and intrinsic information that have strong spatial and contextual (i.e., experience-dependent) features, thereby validating the term *spatial context* when referring to the informational content of place fields (Nadel et al., 1985; Mizumori et al., 1999, 2000; Jeffery et al., 2004). If this information indeed underlies the effective use and generation of episodic memories, Nadel (2008) has argued that the neural representations that define a familiar context must be relatively stable and predictable, maintaining their relationship to each other, until prediction errors are detected. This pattern of place field responses has indeed been documented in the literature. Stable place fields, then, can be said to reflect *the integration of stable background sensory information, internal state or motivational information, as well as response or behavioral outcome expectancies within a spatial framework as a function of time.*

To the extent that different cognitive strategies are mediated by different underlying memories, one network pattern of activated place cells is thought to reflect one memory, and a different pattern of activated place cells corresponds to a different memory (e.g., Samsonovich and McNaughton, 1997). When one refers to place field remapping, then, implicit is the notion that each map (or collection of activated place cells) is driven by a different memory.

SPATIAL CONTEXT DISCRIMINATION AND PREDICTION

As striking as location-selective firing is to even the naive observer, equally impressive is the fact that the otherwise stable place fields readily remap when most any feature of the spatial context changes. This sensitivity to changes in context has led many to suggest that a fundamental operation of the hippocampus is to detect changes in contextual information so that animals can discriminate contexts (e.g., Smith and Mizumori, 2006a,b). The ability to distinguish contexts likely relies on computations that are often attributed to hippocampus, including those that underlie the flexible use of conjunctive, sequential, relational, and spatial algorithms (e.g., O'Keefe and Nadel, 1978; Foster et al., 1987; Eichenbaum et al., 1999; Wood et al., 2000; Eichenbaum and Cohen, 2001; O'Reilly and Rudy, 2001; Fortin et al., 2002). The latter, in turn, are thought to be supported by various forms of pattern separation and pattern completion neurocomputations (Mizumori et al., 2004, 2007b; Penner and Mizumori, 2012a,b).

A *Context Discrimination Hypothesis* (CDH) postulates that single hippocampal neuronal representations of context provide multidimensional data to population-based network computations that ultimately determine whether expected contextual features of a situation have changed (e.g., Mizumori et al., 1999, 2000, 2007a; Smith and Mizumori, 2006a,b; Mizumori, 2008). Initial suggestive evidence of this interpretation of hippocampal network function was the repeated observation that upon less than complete changes in a familiar context, many but not all place fields remap (e.g., Tanila et al., 1997; Mizumori et al., 1999; Brown and Skaggs, 2002; Knierim, 2002; Lee et al., 2004). The place fields that remained in the face of changes in a familiar context were considered to represent the stable or expected contextual features. The place fields that changed, then, could be thought of as representing current context information. The existence of these two types of place field responses gave rise to the notion that hippocampus compares expected and experienced context features (Mizumori et al., 1999). This idea begs the question, then, why does hippocampus represent both expected (learned) and current context information? These hippocampal spatial context representations (O'Keefe and Nadel, 1978; Nadel and Wilner, 1980; Nadel and Payne, 2002) may contribute to a match-mismatch type of analysis that evaluates the present context according to how similar it is to the context that an animal expects to encounter based on past experiences (e.g., Gray, 1982; Vinogradova, 1995; Mizumori et al., 1999, 2000; Gray, 2000; Lisman and Otmakhova, 2001; Hasselmo et al., 2002; Anderson and Jeffery, 2003; Jeffery et al., 2004; Hasselmo, 2005b; Smith and Mizumori, 2006a,b; Manns et al., 2007a; Nadel, 2008). Detected mismatches may be signaled by a change in the pattern of input from hippocampus or possibly by a specific input pattern. This question remains to be answered. Nevertheless, mismatch signals can be used to identify novel situations and to distinguish different contexts, functions that are necessary to define significant events or episodes. Mismatch signals also may engage neural mechanisms that determine the value of the mismatch so that existing memories can be updated and/or new memories can be formed. When context match signals are generated, the effect could be to strengthen currently active memory networks located elsewhere in the brain (e.g., neocortex). In this way, hippocampus may play different mnemonic roles depending on whether or not contexts actually change.

In support of the CDH, disconnecting hippocampus by fornix lesions impairs context discrimination (Smith et al., 2004), and hippocampal lesions reduce animals' ability to respond to changes in a familiar environment (Good and Honey, 1991; Save et al., 1992a,b). Spatial novelty detection corresponds to selective elevation of the immediate early gene c-*fos* in hippocampus, and not in surrounding parahippocampal cortical regions (Jenkins et al., 2004). Also, as described above, hippocampal neurons show significantly altered firing patterns when rats experience spatial or non-spatial changes in a familiar environment (O'Keefe, 1976; Muller and Kubie, 1987; Wood et al., 1999; Fyhn et al., 2002; Ferbinteanu and Shapiro, 2003; Moita et al., 2004; Yeshenko et al., 2004; Leutgeb et al., 2005a,b; Puryear et al., 2006; Smith and Mizumori, 2006b; Eschenko and Mizumori, 2007). As an example, Smith and Mizumori (2006b) showed that hippocampal neurons develop context-specific responses only when rats were required to discriminate contexts. Discriminating neural responses were not observed when rats were allowed to randomly forage for the same amount of time. Further, Manns et al. (2007b) demonstrated that relative to match trials in an odor cue or object recognition task, CA1 neurons preferentially discharged when animals experienced

a non-match situation in these same tasks. Also consistent with the CDH, neuroimaging studies of human performance shows that hippocampus becomes differentially active during match and mismatch trials (Kumaran and Maguire, 2007; Kuhl et al., 2010; Chen et al., 2011; Dickerson et al., 2011; Foerde and Shohamy, 2011; Duncan et al., 2012a,b).

The detection of changes in context is fundamentally important for the continual selection of appropriate behaviors that optimize performance and learning in a variety of tasks (e.g., navigation-based learning, instrumental conditioning, or classical conditioning). Context discrimination engages and prepares cellular mechanisms for rapid and new learning at potentially important times (Paulsen and Moser, 1998), as it is generally known that novelty detection increases attention and exploratory behaviors in a variety of tasks. Interestingly, hippocampal cell firing tends to occur during the "encoding phase" of the ongoing theta rhythm (Hasselmo, 2005a), which is increased during exploratory and investigatory behaviors (Vanderwolf, 1969). Thus, detection of a non-match situation can change the relationship between cell discharge and the local theta rhythm such that encoding functions are enhanced. Detection of matches, on the other hand, does not cause changes in the hippocampal neural activity profile, resulting in efferent messages that continue to retrieve/utilize the currently active memory network that recently drove the execution of successful responses. Context discrimination, then, can be viewed as being critical for the formation of new episodic memories because it leads to the separation in time and space one meaningful event from the next. Such division of memories could facilitate long-term information storage according to memory schemas (Tse et al., 2007; Bethus et al., 2010).

Since hippocampus seems particularly sensitive to changes in the expected (i.e., experience-dependent) context-defining features of a situation, its mismatch signals can be considered to reflect errors in predicted encounters with contextual features, or *context prediction errors*. Indeed, it has been shown that the greater the change in familiar context information, the more place fields remap (e.g., Leutgeb et al., 2005a). It should be noted, however, that when hippocampal cells respond differently to two contexts, it may be because they receive different afferent signals when animals experience different contexts. A second possibility is that the hippocampus receives input from memories stores that define context expectations, and this is actively compared within hippocampus to different input that defines the current context. The simultaneous presence of both familiar and new context information in hippocampus supports the latter possibility. In either case, however, transmission of a context prediction error signal from hippocampus may inform distal brain areas that a change in the context has occurred. Upon receipt of the context prediction error message, efferent midbrain-striatal structures may respond with changes in excitation or inhibition that reflect preparations for, or actual evaluation of, the subjective value of the context prediction error signal (e.g., Mizumori et al., 2004; Lisman and Grace, 2005; Humphries and Prescott, 2010; Penner and Mizumori, 2012a). On the other hand, a hippocampal signal indicating that there was no prediction error may enable plasticity mechanisms that ultimately allow new information to be incorporated into existing memory schemas (e.g., Mizumori et al., 2007a,b; Tse et al., 2007; Bethus et al., 2010). Thus, hippocampal context analyses become critical for the formation of new episodic memories not only because prediction signals provide a mechanism that separates in time and space one meaningful event from the next, but also because the outcome of the prediction error computation engages appropriate neuroplasticity mechanisms in efferent structures that promote subsequent adaptive decisions and memory.

The midbrain dopaminergic system is part of a neural network that assesses the value of behavioral outcomes. Reward-induced excitation of dopamine neurons scales to the magnitude of expected and encountered rewards regardless of the task demands (Schultz et al., 1997; Puryear et al., 2010; Jo et al., 2013): encounters with large rewards are accompanied by larger amplitude phasic dopamine responses than encounters with small amounts of reward. In addition, dopamine cells respond to unexpected reward absences by decreasing their firing rates (Schultz et al., 1997; Puryear et al., 2010). The reduction in firing when rewards are unexpectedly absent is greater if the expectation was for a large, and not small, reward. Further, these reward responses are context-dependent in a manner similar to what is observed for hippocampal place fields (Puryear et al., 2010), a result consistent with the view that hippocampal information guides reward value assessment systems of the brain (e.g., Mizumori et al., 2004; Lisman and Grace, 2005; Puryear et al., 2010) such that the significance of context prediction error messages can be determined (e.g., Penner and Mizumori, 2012a,b). The outcome of the value determination may ultimately come to bias future behavioral responding so that desired goals are more likely to be achieved (see review in Penner and Mizumori, 2012b).

CONTEXT-DEPENDENT TEMPORAL INFORMATION PROCESSING AND EPISODIC MEMORY

Different episodic memories contain information within unique spatial and temporal domains (Tulving, 2002). While there is growing clarity regarding how and why hippocampal neurons represent spatial context information (e.g., Knierim et al., 2006; McNaughton et al., 2006; Penner and Mizumori, 2012a,b; Pilly and Grossberg, 2012; Buzsaki and Moser, 2013), the mechanisms by which spatial context-defined events are distinguished temporally in the service of episodic memory functions remains unclear. However, current evidence support the hypothesis that hippocampus contains an organization structure that permits grouping of information into a number of different time scales (e.g., as reviewed in Buzsaki, 2006; Lisman and Redish, 2009; Grossberg and Pilly, 2013), that are relevant for comparing expected and experienced context information, and thus for episodic memory.

The activity of single neurons and neural networks naturally oscillate within hippocampus and across the brain according to a range of frequencies from low (e.g., 2–4 Hz) to high (e.g., 80 Hz) (Buzsaki, 2006). Oscillatory activity reflects alternating periods of synchronous neural firing: synchronous activity is associated with greater synaptic plasticity and stronger coupling amongst cells of an ensemble, while desynchronous periods are associated with less plasticity and weak signal strength (Hasselmo et al., 2002; Hasselmo, 2005a; Buzsaki, 2006). Thus, inherent in oscillatory neural activity is the ability to segregate on a (very short) time scale the processing of event-related information. In fact, the precise

temporal alignment of place cell firing relative to the phase of the ongoing (theta) rhythm processes as animals move through the cell's place field (referred to as *phase precession*; O'Keefe and Recce, 1993) suggests the possibility that *context-dependent changes in place cell activity alters the state of synaptic plasticity in hippocampus according to experience.* By extension, then, an important impact of altered contextual features is the corresponding change in the nature and/or efficiency of information read into and passed on from hippocampus. Importantly, hippocampal oscillations may enable more temporally precise context representations, and therefore episodic memory. This in turn may enable more precise detection of unexpected context information.

Hippocampal circuits are also observed to synchronize their activity at frequencies greater than the theta frequency. Of particular interest is the gamma band (30–80 Hz) which has been observed in many sensory and motor areas of cortex, hippocampus, parietal cortex, and striatum (e.g., Leung and Yim, 1993; Brosch et al., 2002; Csicsvari et al., 2003; Berke et al., 2004; Bauer et al., 2006; Hoogenboom et al., 2006; Womelsdorf et al., 2006). Orchestration of both excitatory and inhibitory networks within each structure underlies the generation of synchronized gamma oscillations (e.g., Whittington et al., 1995; Vida et al., 2006). Although the functional importance of gamma oscillations remains debated, information carried by the cells that participate in a gamma-burst is effectively accentuated against a background of disorganized neural activity. Therefore, it has been suggested that gamma-bursts represent a fundamental mechanism by which information becomes segmented, filtered, or highlighted within a structure, as well as a mechanisms by which to coordinate information across structures (Buzsaki, 2006). Theta and gamma have many common physiological and behavioral relationships, suggesting that they are components of a coordinated and larger scale oscillatory network. For example, similar to theta rhythms, single unit responses that are recorded simultaneously with gamma oscillations have been found to have specific phase relationships to the gamma rhythm, and both theta and gamma are at least in part regulated by dopamine (e.g., Berke, 2009; van der Meer and Redish, 2009; Kalenscher et al., 2010). Therefore, changes in context that induce remapping (i.e., that altered the constellation of activated neurons), likely change patterns of gamma activity that are characteristic of a familiar context. Since gamma oscillations may effectively select salient information that ultimately impacts decisions, learning, and behavioral responses (e.g., van der Meer and Redish, 2009; Kalenscher et al., 2010), it is predicted that changes in gamma oscillatory patterns are likely to alter future decisions and learning. Further, gamma-bursts should become more predictable as learning takes place within a given context. *The relationship between place fields and the overriding theta and gamma rhythms is then an important mechanism by which spatially organized context information becomes temporally organized as animals experience an environment* (Buzsaki, 2006; Buzsaki and Moser, 2013). Specifically, this type of temporal relationship may confer a high level of temporal alignment (and hence accuracy) between expected and experienced context information, and this in turn should increase the accuracy of their comparison.

Since multiple brain areas demonstrate rhythmic neural activity, neural oscillations are likely a fundamental mechanism for coordinating neural activity across the brain in the service of adaptive decisions, learning, and memory (e.g., Buzsaki, 2006; Fries, 2009; Monaco et al., 2011; Penner and Mizumori, 2012b). Numerous laboratories have now reported that synchronous neural activity (in particular coherence of the theta rhythm) can be detected within and between memory-related brain structures such as the hippocampus, striatum, or prefrontal cortex (Tabuchi et al., 2000; Engel et al., 2001; Fell et al., 2001; Varela et al., 2001; Siapas et al., 2005; DeCoteau et al., 2007a; Womelsdorf et al., 2007). For example, hippocampal theta activity can become synchronized with place cell firing, resulting in coordinated timing of spatial coding (O'Keefe and Recce, 1993; Gengler et al., 2005). Also, theta oscillations within the striatum can become entrained to the hippocampal theta rhythm (Berke et al., 2004; DeCoteau et al., 2007a). Stimulating the striatum can induce hippocampal theta activity (Sabatino et al., 1985) and increases high frequency theta power, which is thought to be important for sensorimotor integration (Hallworth and Bland, 2004). Also, hippocampal and striatal activity theta activity become increasingly coherent during goal-directed navigation (Allers et al., 2002; DeCoteau et al., 2007a). When neural activity is disrupted in the striatum via D2 receptor antagonism, striatal modulation of high frequency hippocampal theta activity is also disrupted. The result is that motor and spatial/contextual information is not integrated, and task performance is impaired (Gengler et al., 2005).

Particularly intriguing is a finding common to both hippocampus and striatum, and that is that synchronous activity occurs in specific task-relevant ways (e.g., Hyman et al., 2005; Jones and Wilson, 2005) particularly during times when rats are said to be engaged in decision making (e.g., Benchenane et al., 2010). For example, striatal theta is modified over the course of learning on an egocentric T-maze task, increasing in coherence as the rat chooses and initiates turn behavior (DeCoteau et al., 2007a,b). Rats that learn the task develop an antiphase relationship between hippocampal and striatal theta oscillations, while rats that do not learn the task also do not show this type of theta relationship. This coherence has also been observed during striatal-dependent classical conditioning (Kropf and Kuschinsky, 1993). Coherent theta oscillations across distant brain structures can be enhanced with application of dopamine (Benchenane et al., 2010). Dopamine, then, may play a crucial role in coordinating ensemble activity across brain areas during times of decision making during navigation. Functionally, this type of control by dopamine suggests that information about the saliency of reward may determine which brain systems become synchronized (and desynchronized). This in turn guides the nature and type of information that is used to update memories and to determine future responses.

Task demands, then, seem to dictate the nature of neural synchrony across distal brain structures, and this synchrony may take the form of comodulation of existing theta and gamma rhythms as well as the generation of an additional rhythm. The latter was illustrated in a recent study by Fujisawa and Buzsaki (2011). They demonstrated that the existence of very low frequency (4 Hz) entrainment of local field potentials, e.g., the 7–12 Hz theta oscillation, that emerges only during phases of a maze task when rats made decisions (i.e., in the stem of a T-Maze). During decision periods, the 4 Hz rhythm was phase locked to theta oscillations

in both the prefrontal cortex and VTA. Some of the individual prefrontal and VTA neurons were also phase locked to hippocampal theta oscillation at this time. Importantly the 4 Hz rhythm was present only during a decision making period when theta oscillations were also present. The findings of this study suggest that a 4 Hz rhythm may coordinate activity in distal brains structures specifically as animals make decisions during goal-directed navigation.

Assuming that "orchestrating" rhythms such as the 4 Hz rhythm also incorporate hippocampal neural activity, place field remapping is expected to have effects that extend well beyond hippocampal computations. When an expected context changes, evidence shows that place fields change by either increasing or decreasing firing rates and/or changes in their spatial specificity and reliability. This period of place field change corresponds to the period of uncertainty that is generated with by the context change. Therefore, as uncertainty decreases, place fields become more stable, and this in turn should result in the generation of more stable comodulation of specific frequencies of EEG across brain structures.

To fully understand the role of the hippocampus in episodic memory requires an understanding of how hippocampus relates event-specific details to particular temporal features of a task. Recently many (Manns et al., 2007b; Pastalkova et al., 2008; Gill et al., 2011; McDonald et al., 2011; Kraus et al., 2013) have suggest the existence of "time cells" in addition to place cells in hippocampus. These studies demonstrate that the timing of cell firing by a subpopulation of hippocampal neurons is not directly related to spatial or behavioral metrics such as distance, location, or running speed but rather they appear tuned to the timing of task-relevant events. Another challenge for future research is to better define how hippocampal context prediction error signals are interpreted and valued by neural systems responsible for decisions based on the most recent context analysis, and ultimately, by neural systems that update memories (Lisman and Grace, 2005; Penner and Mizumori, 2012a,b). The midbrain dopaminergic system is likely involved in this assessment process since dopamine neurons are not only known to respond to changes in the learned value of rewards, and to cues that predict future rewards (Schultz et al., 1997), but also they respond to changes in reward values in a context-dependent manner when rats perform a hippocampal-dependent task (Puryear et al., 2010).

Dopamine neural responses to the expectation of rewards seem to be regulated at least in part by prefrontal cortex (Jo et al., 2013), suggesting that the prefrontal cortex may relay to dopamine neurons information based on stored memories about past consequences of behavior. Penner and Mizumori (2012b) recently reviewed an extensive literature that describes how dopamine cell responses to hippocampal-based context information can come to regulate subsequent choices and response selection as information is processed through iterative striatal-to-cortex information loops (Haber et al., 2000). The result of this sequence of striatal-cortical processing is the determination of the degree to which expected behavioral outcomes occurred, and the updating of long-term memory. The latter, in turn, updates the definition of expected context features that cortex subsequently provides hippocampus (Penner and Mizumori, 2012a,b; Mizumori and Jo, 2013). Indeed Martig and Mizumori (2011) have shown that inactivation of the VTA results in unstable hippocampal place fields and behavioral errors when rats perform a hippocampal-dependent spatial task. Since the outcome assessment by VTA impacts the subsequent stability of hippocampal neural codes and behavioral accuracy on a spatial working memory task, it is likely that hippocampus and the VTA-striatal circuitry comprise key components of an adaptive loop of neural processing that allows organisms to continuously update memories and memory representations according to the outcomes of choices made within circumscribed epochs of time.

HOMEOSTATIC REGULATION OF NEURAL SIGNALS OF PREDICTION ERRORS

An emerging view is that the brain has evolved in large part to allow organisms to accurately predict the outcomes of events and behaviors (e.g., Llinas and Roy, 2009; Buzsaki, 2013; Buzsaki and Moser, 2013; Mizumori and Jo, 2013). More specifically, it has been suggested that organisms have been able to adapt to environments and societies of increasing complexity because brains evolved more complex neural circuitry that support the ability to make dynamic and conditional decisions and predictions. These neural ensembles evolved to retain information over times of varying scales depending on the desired goal. Different brain areas are known to generate and retain sequences of information, and this ability can be accounted for by state-dependent changes in network dynamics (Mauk and Buonomano, 2004), internally generated oscillatory activity (Pastalkova et al., 2008), and/or dedicated "time cells" (Kraus et al., 2013). Thus, many elemental features of prediction analyses seem to be intrinsic, or self-generated. This property is likely very important for it may provide a mechanism by which prediction analyses can occur automatically so that organisms naturally seek control of the outcomes to their behaviors. What, then, might be the mechanism of a self-generated, and thus auto-regulated, brain prediction system? It is suggested here that such a mechanism may to some extent mirror principles of self-regulation at synaptic and neural circuit levels (e.g., Turrigiano, 1999, 2008, 2011; Marder and Prinz, 2003; Turrigiano and Nelson, 2004; Marder and Goaillard, 2006; Shetty et al., 2012; Mizumori and Jo, 2013).

Marder and Goaillard (2006) suggested that homeostatic neuroplasticity may be nested: calcium sensors may monitor neural firing rates, then up or down regulate the availability of glutamate receptors to ramp up or down firing rates toward an optimal firing rate set point. Groups of neurons or neural networks may sense changes in firing collectively to regulate experience-dependently population activity levels and patterns of activation. In this way homeostatic plasticity enables groups of neural circuits to find a balance between flexible and stable processing as needed to learn from experiences, and to be responsive to future changed inputs. The details of how networks of cells or their connections engage in homeostatic regulation remain to be discovered. Nevertheless, it is worth noting that homeostatic regulation at the neural systems level is clearly evident from studies of brain development, as well as from studies of reactive or compensatory neuroplasticity mechanisms that occur in response to experience (e.g., sensorimotor learning; Froemke et al., 2007) or brain injury (e.g., brain trauma or addiction; Robinson and Kolb, 2004; Nudo,

2011). While specific homeostatic neural plasticity mechanisms have not been used to account for complex learning, current theories of reinforcement- and context-based learning and memory commonly rely on the autoregulation of feedback loops.

A homeostatic framework could apply to the autoregulation of prediction analyses, which in turn will impact regulation of future decisions and memories. Such a framework includes *variables* that are monitored by *sensors* and then regulated by *controllers*, and thus it likely involves multiple, interactive, and hierarchically organized (auto-regulated) information loops analogous to what was described by Buzsaki (2013). At the cellular or synaptic levels, homeostatic plasticity mechanisms (Turrigiano et al., 1998; Marder and Goaillard, 2006; Turrigiano, 2011) may regulate cell excitability around a neural activity *set point* such that neurons retain maximal responsivity to future inputs. This process enables neurons to achieve a balance between synaptic stability and flexibility. Changes in calcium flux appear to be an important part of the sensing system that determines the current level of firing. It is hypothesized here that a prediction error, or mismatch signal, may result in higher or lower firing rates, at which time *controller* mechanisms should be engaged to bring the firing rates back to set point levels. Indeed reward prediction errors are illustrated by transient and significant reduced or elevated neural firing depending on the valence of the error (Schultz et al., 1997). Future research should focus on understanding the enabling and restorative mechanisms of prediction error signals. Of particular interest are mechanisms by which cortical memory may impact the threshold for signaling prediction errors. One cortical area of interest is the prefrontal cortex given (a) its intrinsic recurrent circuitry and detailed excitatory and inhibitory extrinsic connections (as reviewed in Arnsten et al., 2012) with both hippocampal/temporal lobe and reward valuation systems, and (b) given its role in attention and working memory (e.g., Fuster, 2006, 2008, 2009). That is, prefrontal cortex may orchestrate and coordinate the level of neural excitability in different prediction error brain areas according to homeostatic principles and in this way, bias the nature of the outputs of connected brain areas according to experience and recent outcomes of decisions. Prefrontal cortex also has strong functional connections with other cortical memory areas (e.g., parietal and temporal cortex), and is thus strategically positioned to influence long-term memory updating based on prediction error analyses. In this way the most recent memories can be fed forward to hippocampus for future context evaluation.

Although it is reasonable to assume that the prefrontal cortex controls or biases neural signaling in distal prediction brain regions, it should be noted that other sources of control of cell excitability may arise via direct interconnections amongst the multiple prediction detection areas of the brain. For example, a prediction error signal from the hippocampus could be transmitted to midbrain-striatal neurons along pathways that do not necessarily include the prefrontal cortex. Indirect support for this idea come from observations that conditions that produce error messages in the hippocampus change reward responses of dopamine neurons (Puryear et al., 2010; Jo et al., 2013), phasic theta comodulation is observed between hippocampus and striatum (DeCoteau et al., 2007a) during decision tasks, and comodulation of neural activity has been reported between prefrontal cortex and parietal cortex (Diwadkar et al., 2000). However, the identification of such correlations does not necessarily mean that this is the source of the comodulation or neural synchrony. Finding the source of neural regulation remains a challenge for the general field of systems neuroscience, one that may soon have answers with continued development of new methodologies such as optogenetic analyses.

In sum, homeostatic regulatory processes may contribute to the automatic and continuous self-regulatory nature of prediction error analysis, and ultimately decision making and episodic memory. Such a naturally adaptive mechanism optimizes the contribution of different types of prediction error signals to future decisions and actions according to the pattern of recent successes and failures in prediction.

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REFERENCES

Allers, K. A., Ruskin, D. N., Bergstrom, D. A., Freeman, L. E., Ghazi, L. J., Tierney, P. L., et al. (2002). Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. *J. Neurophysiol.* 87, 1118–1122.

Anagnostaras, S. G., Gale, G. D., and Fanselow, M. S. (2001). Hippocampus and contextual fear conditioning: recent controversies and advances. *Hippocampus* 11, 8–17. doi:10.1002/1098-1063(2001)11:1<8::AID-HIPO1015>3.3.CO;2-Z

Anderson, M. I., and Jeffery, K. J. (2003). Heterogeneous modulation of place cell firing by changes in context. *J. Neurosci.* 23, 8827–8835.

Arnsten, A. F. T., Wang, M. J., and Paspalas, C. D. (2012). Neuromodulation of thought: flexibilities and vulnerabilities in prefrontal cortical network synapses. *Neuron* 76, 223–239. doi:10.1016/j.neuron.2012.08.038

Bauer, M., Oostenveld, R., Peeters, M., and Fries, P. (2006). Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. *J. Neurosci.* 26, 490–501. doi:10.1523/JNEUROSCI.5228-04.2006

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., et al. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron* 66, 921–936. doi:10.1016/j.neuron.2010.05.013

Berke, J. D. (2009). Fast oscillations in cortical-striatal networks switch frequency following rewarding events and stimulant drugs. *Eur. J. Neurosci.* 30, 848–859. doi:10.1111/j.1460-9568.2009.06843.x

Berke, J. D., Okatan, M., Skurski, J., and Eichenbaum, H. B. (2004). Oscillatory entrainment of striatal neurons in freely moving rats. *Neuron* 43, 883–896. doi:10.1016/j.neuron.2004.08.035

Bethus, I., Tse, D., and Morris, R. G. (2010). Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *J. Neurosci.* 30, 1610–1618. doi:10.1523/JNEUROSCI.2721-09.2010

Bouton, M. E., Westbrook, R. F., Corcoran, K. A., and Maren, S. (2006). Contextual and temporal modulation of extinction: behavioral and biological mechanisms. *Biol. Psychiat.* 60, 352–360. doi:10.1016/j.biopsych.2005.12.015

Brosch, M., Budinger, E., and Scheich, H. (2002). Stimulus-related gamma oscillations in primate auditory cortex. *J. Neurophysiol.* 87, 2715–2725.

Brown, J. E., and Skaggs, W. E. (2002). Concordant and discordant coding of spatial location in populations of hippocampal CA1 pyramidal cells. *J. Neurophysiol.* 88, 1605–1613.

Buzsaki, G. (2006). *Rhythms of the Brain.* New York: Oxford Press.

Buzsaki, G. (2013). Time, space and memory. *Nature* 497, 568–569. doi:10.1038/497568a

Buzsaki, G., and Moser, E. I. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat. Neurosci.* 16, 130–138. doi:10.1038/nn.3304

Chen, J., Olsen, R. K., Preston, A. R., Glover, G. H., and Wagner, A. D. (2011). Associative retrieval processes in the human medial temporal lobe: hippocampal retrieval success and CA1 mismatch detection. *Learn. Mem.* 18, 523–528. doi: 10.1101/lm.2135211

Csicsvari, J., Jamieson, B., Wise, K. D., and Buzsaki, G. (2003). Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* 37, 311–322. doi:10.1016/S0896-6273(02)01169-8

DeCoteau, W. E., Thorn, C., Gibson, D. J., Courtemanche, R., Mitra, P., Kubota, Y., et al. (2007a). Learning-related coordination of striatal and hippocampal theta rhythms during acquisition of a procedural maze task. *Proc. Natl. Acad. Sci. U.S.A.* 104, 5644–5649. doi:10.1073/pnas.0700818104

DeCoteau, W. E., Thorn, C., Gibson, D. J., Courtemanche, R., Mitra, P., Kubota, Y., et al. (2007b). Oscillations of local field potentials in the rat dorsal striatum during spontaneous and instructed behaviors. *J. Neurophysiol.* 97, 3800–3805. doi:10.1152/jn.00108.2007

Dickerson, K. C., Li, J., and Delgado, M. R. (2011). Parallel contributions of distinct human memory systems during probabilistic learning. *Neuroimage* 55, 266–276. doi:10.1016/j.neuroimage.2010.10.080

Diwadkar, V. A., Carpenter, P. A., and Just, M. A. (2000). Collaborative activity between parietal and dorso-lateral prefrontal cortex in dynamic spatial working memory revealed by fMRI. *Neuroimage* 12, 85–99. doi:10.1006/nimg.2000.0586

Duncan, K., Ketz, N., Inati, S. J., and Davachi, L. (2012a). Evidence for area CA1 as a match/mismatch detector: a high-resolution fMRI study of the human hippocampus. *Hippocampus* 22, 389–398. doi:10.1002/hipo.20933

Duncan, K., Sadanand, A., and Davachi, L. (2012b). Memory's penumbra: episodic memory decisions induce lingering mnemonic biases. *Science* 337, 485–487. doi:10.1126/science.1221936

Eichenbaum, H., and Cohen, N. J. (2001). *From Conditioning to Conscious Recollection: Memory Systems of the Brain*. New York: Oxford University Press.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., and Tanila, H. (1999). The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron* 425, 184–188.

Engel, A. K., Fries, P., and Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* 2, 704–716. doi:10.1038/35094565

Eschenko, O., and Mizumori, S. J. (2007). Memory influences on hippocampal and striatal neural codes: effects of a shift between task rules. *Neurobiol. Learn Mem.* 87, 495–509. doi:10.1016/j.nlm.2006.09.008

Fanselow, M. S., and Poulos, A. M. (2005). The neuroscience of mammalian associative learning. *Annu. Rev. Psychol.* 56, 207–234. doi:10.1146/annurev.psych.56.091103.070213

Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C. E., et al. (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nat. Neurosci.* 4, 1259–1264. doi:10.1038/nn759

Ferbinteanu, J., and Shapiro, M. L. (2003). Prospective and retrospective memory coding in the hippocampus. *Neuron* 40, 1227–1239. doi:10.1016/S0896-6273(03)00752-9

Foerde, K., and Shohamy, D. (2011). Feedback timing modulates brain systems for learning in humans. *J. Neurosci.* 31, 13157–13167. doi:10.1523/JNEUROSCI.2701-11.2011

Fortin, N. J., Agster, K. L., and Eichenbaum, H. B. (2002). Critical role of the hippocampus in memory for sequences of events. *Nat. Neurosci.* 5, 458–462.

Foster, T. C., Christian, E. P., Hampson, R. E., Campbell, K. A., and Deadwyler, S. A. (1987). Sequential dependencies regulate sensory evoked responses of single units in the rat hippocampus. *Brain Res.* 408, 86–96. doi:10.1016/0006-8993(87)90361-1

Freeman, J. H. Jr., Cuppernell, C., Flannery, K., and Gabriel, M. (1996a). Context-specific multi-site cingulate cortical, limbic thalamic, and hippocampal neuronal activity during concurrent discriminative approach and avoidance training in rabbits. *J. Neurosci.* 16, 1538–1549.

Freeman, J. H. Jr., Cuppernell, C., Flannery, K., and Gabriel, M. (1996b). Limbic thalamic, cingulate cortical and hippocampal neuronal correlates of discriminative approach learning in rabbits. *Behav. Brain Res.* 80, 123–136. doi:10.1016/0166-4328(96)00027-7

Fries, P. (2009). Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci.* 32, 209–224. doi:10.1146/annurev.neuro.051508.135603

Froemke, R. C., Merzenich, M. M., and Schreiner, C. E. (2007). A synaptic memory trace for cortical receptive field plasticity. *Nature* 450, 425–429. doi:10.1038/nature06289

Fujisawa, S., and Buzsaki, G. (2011). A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. *Neuron* 72, 153–165. doi:10.1016/j.neuron.2011.08.018

Fuster, J. M. (2006). The cognit: A network model of cortical representation. *Int. J. Psychophysiol.* 60, 125–132. doi:10.1016/j.ijpsycho.2005.12.015

Fuster, J. M. (2008). *The Prefrontal Cortex, Fourth Edition*. London: Academic Press.

Fuster, J. M. (2009). Cortex and memory: emergence of a new paradigm. *J. Cog. Neurosci.* 21, 2047–2072. doi:10.1162/jocn.2009.21280

Fyhn, M., Molden, S., Hollup, S., Moser, M. B., and Moser, E. (2002). Hippocampal neurons responding to first-time dislocation of a target object. *Neuron* 35, 555–566. doi:10.1016/S0896-6273(02)00784-5

Gengler, S., Mallot, H. A., and Holscher, C. (2005). Inactivation of the rat dorsal striatum impairs performance in spatial tasks and alters hippocampal theta in the freely moving rat. *Behav. Brain Res.* 164, 73–82. doi:10.1016/j.bbr.2005.06.009

Gill, P. R., Mizumori, S. J. Y., and Smith, D. M. (2011). Hippocampal episode fields develop with learning. *Hippocampus* 21, 1240–1249. doi:10.1002/hipo.20832

Good, M., and Honey, R. C. (1991). Conditioning and contextual retrieval in hippocampal rats. *Behav. Neurosci.* 105, 499–509. doi:10.1037/0735-7044.105.4.499

Gothard, K. M., Skaggs, W. E., Moore, K. M., and Mcnaughton, B. L. (1996). Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J. Neurosci.* 16, 823–835.

Gray, J. A. (1982). *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocamal System*. Oxford: Oxford University Press.

Gray, J. A. (2000). *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocamal System*, 2nd Edn. Oxford: Oxford University Press.

Grossberg, S., and Pilly, P. K. (2013). How entorhinal grid cells may learn multiple spatial scales from a dorsoventral gradient of cell response rates in a self-organizing map. *PLoS Comput. Biol.* 8:e1002648. doi:10.1371/journal.pcbi.1002648

Haber, S. N., Fudge, J. L., and McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* 20, 2369–2382.

Hallworth, N. E., and Bland, B. H. (2004). Basal ganglia – hippocampal interactions support the role of the hippocampal formation in sensorimotor integration. *Exp. Neurol.* 188, 430–443. doi:10.1016/j.expneurol.2004.04.014

Hasselmo, M. E. (2005a). What is the function of hippocampal theta rhythm? – Linking behavioral data to phasic properties of field potential and unit recording data. *Hippocampus* 15, 936–949. doi:10.1002/hipo.20116

Hasselmo, M. E. (2005b). The role of hippocampal regions CA3 and CA1 in matching entorhinal input with retrieval of associations between objects and context: theoretical comment on Lee etal. (2005). *Behav. Neurosci.* 119, 342–345. doi:10.1037/0735-7044.119.1.342

Hasselmo, M. E., Hay, J., Ilyn, M., and Gorchetchnikov, A. (2002). Neuromodulation, theta rhythm and rat spatial navigation. *Neural Netw.* 15, 689–707. doi:10.1016/S0893-6080(02)00057-6

Hirsh, R. (1974). The hippocampus and contextual retrieval of information from memory: a theory. *Behav. Biol.* 12, 421–444. doi:10.1016/S0091-6773(74)92231-7

Hoogenboom, N., Schoffelen, J. M., Oostenveld, R., Parkes, L. M., and Fries, P. (2006). Localizing human visual gamma-band activity in frequency, time and space. *Neuroimage* 29, 764–773. doi:10.1016/j.neuroimage.2005.08.043

Humphries, M. D., and Prescott, T. J. (2010). The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. *Prog. Neurobiol.* 90, 385–417. doi:10.1016/j.pneurobio.2009.11.003

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2005). Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior.

Hippocampus 15, 739–749. doi:10.1002/hipo.20106

Jeffery, K. J., Anderson, M. I., Hayman, R., and Chakraborty, S. (2004). A proposed architecture for the neural representation of spatial context. *Neurosci. Biobehav. Rev* 28, 201–218. doi:10.1016/j.neubiorev.2003.12.002

Jenkins, T. A., Amin, E., Pearce, J. M., Brown, M. W., and Aggleton, J. P. (2004). Novel spatial arrangements of familiar visual stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a c-fos expression study. *Neuroscience* 124, 43–52. doi:10.1016/j.neuroscience.2003.11.024

Jo, Y. S., Lee, J., and Mizumori, S. J. Y. (2013). Effects of prefrontal cortical inactivation on neural activity in the ventral tegmental area. *J. Neurosci.* 33, 8159–8171. doi:10.1523/JNEUROSCI.0118-13.2013

Jones, M. W., and Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3:e402. doi:10.1371/journal.pbio.0030402

Kalenscher, T., Lansink, C. S., Lankelma, J. V., and Pennartz, C. M. (2010). Reward-associated gamma oscillations in ventral striatum are regionally differentiated and modulate local firing activity. *J. Neurophysiol.* 103, 1658–1672. doi:10.1152/jn.00432.2009

Kim, J. J., and Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science* 256, 675–677. doi:10.1126/science.1585183

Knierim, J. J. (2002). Dynamic interactions between local surface cues, distal landmarks, and intrinsic circuitry in hippocampal place cells. *J. Neurosci.* 22, 6254–6264.

Knierim, J. J., Lee, I., and Hargreaves, E. L. (2006). Hippocampal place cells: parallel input streams, subregional processing and implications for episodic memory. *Hippocampus* 16, 755–764. doi:10.1002/hipo.20203

Kraus, B. J., Robinson, R. J. II, White, J. A., Eichenbaum, H., and Hasselmo, M. E. (2013). Hippocampal "time cells": time versus path integration. *Neuron* 78, 1–12. doi:10.1016/j.neuron.2013.04.015

Kropf, W., and Kuschinsky, K. (1993). Conditioned effects of apomorphine are manifest in regional EEG of rats both in hippocampus and in striatum. *Naunyn Schmiedebergs Arch. Pharmacol.* 347, 487–493. doi:10.1007/BF00166740

Kuhl, B. A., Shah, A. T., DuBrow, S., and Wagner, A. D. (2010). Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. *Nat. Neurosci.* 13, 501–506. doi:10.1038/nn.2498

Kumaran, D., and Maguire, E. A. (2007). Match-mismatch processes underlie human hippocampal responses to associative novelty. *J. Neurosci.* 27, 8517–8524. doi:10.1523/JNEUROSCI.1677-07.2007

Lee, I., Yognarasimha, D., Rao, G., and Knierim, J. J. (2004). Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. *Nature* 430, 456–459. doi:10.1038/nature02739

Leung, L. S., and Yim, C. Y. (1993). Rhythmic delta-frequency activities in the nucleus accumbens of anesthetized and freely moving rats. *Can. J. Physiol. Pharmacol.* 71, 311–320. doi:10.1139/y93-049

Leutgeb, J. K., Leutgeb, S., Treves, A., Meyer, R., Barnes, C. A., McNaughton, B. L., et al. (2005a). Progressive transformation of hippocampal neuronal representations in "morphed" environments. *Neuron* 48, 345–358. doi:10.1016/j.neuron.2005.09.007

Leutgeb, S., Leutgeb, J. K., Barnes, C. A., Moser, E. I., McNaughton, B. L., and Moser, M. B. (2005b). Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* 309, 619–623. doi:10.1126/science.1114037

Lisman, J. E., and Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 46, 703–713. doi:10.1016/j.neuron.2005.05.002

Lisman, J. E., and Otmakhova, N. A. (2001). Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine. *Hippocampus* 11, 551–568. doi:10.1002/hipo.1071

Lisman, J. E., and Redish, A. D. (2009). Prediction, sequences and the hippocampus. *Philos. Trans R. Soc. Lond. B Biol. Sci.* 364, 1193–1201. doi:10.1098/rstb.2008.0316

Llinas, R. R., and Roy, S. (2009). The 'predictive imperative' as the basis for self-awareness. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* 364, 1301–1307. doi:10.1098/rstb.2008.0309

McDonald, C. J., Lepage, K. Q., Eden, U. T., and Eichenbaum, H. (2011). Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron* 71, 737–749. doi:10.1016/j.neuron.2011.07.012

Manns, J. R., Howard, M. W., and Eichenbaum, H. (2007a). Gradual changes in hippocampal activity support remembering the order of events. *Neuron* 56, 530–540. doi:10.1016/j.neuron.2007.08.017

Manns, J. R., Zilli, E. A., Ong, K. C., Hasselmo, M. E., and Eichenbaum, H. (2007b). Hippocampal CA1 spiking during encoding and retrieval: Relation to theta phase. *Neurobiol. Learn. Mem.* 87, 9–20. doi:10.1016/j.nlm.2006.05.007

Marder, E., and Goaillard, J. M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.* 7, 563–574. doi:10.1038/nrn1949

Marder, E., and Prinz, A. A. (2003). Current compensation in neuronal homeostasis. *Neuron* 37, 2–4. doi:10.1016/S0896-6273(02)01173-X

Maren, S. (2001). Neurobiology of Pavlovian fear conditioning. *Ann. Rev. Neurosci.* 24, 897–931. doi:10.1146/annurev.neuro.24.1.897

Martig, A. K., and Mizumori, S. J. (2011). Ventral tegmental area disruption selectively affects CA1/CA2 but not CA3 place fields during a differential reward working memory task. *Hippocampus* 21, 172–184. doi:10.1002/hipo.20734

Mauk, M. D., and Buonomano, D. V. (2004). The neural basis of temporal processing. *Annu. Rev. Neurosci.* 27, 307–340. doi:10.1146/annurev.neuro.27.070203.144247

McEchron, M. C., and Disterhoft, J. F. (1999). Hippocampal encoding of non-spatial trace conditioning. *Hippocampus* 9, 385–396. doi:10.1002/(SICI)1098-1063(1999)9:4<385::AID-HIPO5>3.0.CO;2-K

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., and Moser, M.-B. (2006). Path integration and the neural basis of the 'cognitive map'. *Nat. Rev. Neurosci.* 7, 663–678. doi:10.1038/nrn1932

Mizumori, S. J. Y., Cooper, B. G., Leutgeb, S., and Pratt, W. E. (2000). A neural systems analysis of adaptive navigation. *Mol. Neurobiol.* 21, 57–82. doi:10.1385/MN:21:1-2:057

Mizumori, S. J. Y. (ed.) (2008). *A Context for Hippocampal Place Cells During Learning*. New York: Oxford University Press.

Mizumori, S. J. Y., and Jo, Y. S. (2013). Homeostatic regulation of memory systems and adaptive decisions. *Hippocampus*. doi:10.1002/hipo.22176

Mizumori, S. J. Y., Ragozzino, K. E., Cooper, B. G., and Leutgeb, S. (1999). Hippocampal representational organization and spatial context. *Hippocampus* 9, 444–451. doi:10.1002/(SICI)1098-1063(1999)9:4<444::AID-HIPO10>3.3.CO;2-Q

Mizumori, S. J. Y., Smith, D. M., and Puryear, C. B. (2007a). Hippocampal and neocortical interactions during context discrimination: electrophysiological evidence from the rat. *Hippocampus* 17, 851–862. doi:10.1002/hipo.20317

Mizumori, S. J. Y., Smith, D. M., and Puryear, C. B. (2007b). "Mnemonic contributions of hippocampal place cells," in *Neurobiology of Learning and Memory*, eds J. L. Martinez Jr. and R. P. Kesner (New York: Academic Press), 155–190.

Mizumori, S. J. Y., Yeshenko, O., Gill, K. M., and Davis, D. M. (2004). Parallel processing across neural systems: implications for a multiple memory system hypothesis. *Neurobiol. Learn. Mem.* 82, 278–298. doi:10.1016/j.nlm.2004.07.007

Moita, M. A., Rosis, S., Zhou, Y., LeDoux, J. E., and Blair, H. T. (2004). Putting fear in its place: Remapping of hippocampal place cells during fear conditioning. *J. Neurosci.* 24, 7015–7023. doi:10.1523/JNEUROSCI.5492-03.2004

Monaco, J. D., Knierim, J. J., and Zhang, K. (2011). Sensory feedback, error correction, and remapping in a multiple oscillator model of place-cell activity. *Front. Comput. Neurosci.* 5:1–17. doi:10.3389/fncom.2011.00039

Muller, R. U., and Kubie, J. L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J. Neurosci.* 7, 1951–1968.

Myers, C. E., and Gluck, M. (1994). Context, conditioning, and hippocampal representation in animal learning. *Behav. Neurosci.* 108, 835–847. doi:10.1037/0735-7044.108.5.835

Nadel, L. (2008). "The hippocampus and context revisited," in *Hippocampal Place Fields: Relevance to Learning and Memory*, ed. S. J. Y. Mizumori (New York: Oxford University Press), 3–15.

Nadel, L., and Payne, J. D. (2002). "The hippocampus, way finding and episodic memory," in *The Neural Basis of Navigation: Evidence from Single Cell Recording*, ed. P. E. Sharp (Norwell, MA: Kluwer Academic Publisher), 235–248.

Nadel, L., Willner, J., and Kurz, E. M. (1985). "Cognitive maps and environmental context," in *Context*

and Learning, eds P. Balsam, and A. Tomie (Hillside, NJ: Erlbaum), 385–406.

Nadel, L., and Wilner, J. (1980). Context and conditioning: a place for space. *Physiol. Psychol.* 8, 218–228.

Nudo, R. J. (2011). Neural bases of recovery after brain injury. *J. Commun. Disord.* 44, 515–520. doi:10.1016/j.jcomdis.2011.04.004

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. *Exp. Neurol.* 51, 78–109. doi:10.1016/0014-4886(76)90055-8

O'Keefe, J., and Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature* 381, 425–428. doi:10.1038/381425a0

O'Keefe, J., and Conway, D. H. (1978). Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp. Brain Res.* 31, 573–590. doi:10.1007/BF00239813

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34, 171–175. doi:10.1016/0006-8993(71)90358-1

O'Keefe, J., and Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press.

O'Keefe, J., and Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330. doi:10.1002/hipo.450030307

Olton, D. S., Branch, M., and Best, P. J. (1978). Spatial correlates of hippocampal unit activity. *Exp. Neurol.* 58, 387–409. doi:10.1016/0014-4886(78)90096-1

O'Reilly, R. C., and Rudy, J. W. (2001). Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychol. Rev.* 108, 311–345. doi:10.1037/0033-295X.108.2.311

Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsaki, G. (2008). Internally generated cell assembly sequences in the rat hippocampus. *Science* 321, 1322–1327. doi:10.1126/science.1159775

Paulsen, O., and Moser, E. I. (1998). A model of hippocampal memory encoding and retrieval: GABAergic control of synaptic plasticity. *Trends Neurosci.* 21, 273–278. doi:10.1016/S0166-2236(97)01205-8

Penick, S., and Solomon, P. R. (1991). Hippocampus, context, and conditioning. *Behav. Neurosci.* 105, 611–617. doi:10.1037/0735-7044.105.5.611

Penner, M. R., and Mizumori, S. J. Y. (2012a). Age-associated changes in the hippocampal-ventral striatum-ventral tegmental loop that impact learning, prediction and context discrimination. *Front. Aging Neurosci.* 4:1–12. doi:10.3389/fnagi.2012.00022

Penner, M. R., and Mizumori, S. J. Y. (2012b). Neural systems analysis of decision making during goal-directed navigation. *Prog. Neurobiol.* 96, 96–135. doi:10.1016/j.pneurobio.2011.08.010

Phillips, R. G., and LeDoux, J. E. (1992). Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.* 106, 274–285. doi:10.1037/0735-7044.106.2.274

Phillips, R. G., and LeDoux, J. E. (1994). Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. *Learn Mem.* 1, 34–44. doi:10.1101/lm.1.1.34

Pilly, P. K., and Grossberg, S. (2012). How do spatial learning and memory occur in the brain? Coordinated learning of entorhinal grid cells and hippocampal place cells. *J. Cogn. Neurosci.* 24, 1031–1054. doi:10.1162/jocn_a_00200

Puryear, C. B., Kim, M. J., and Mizumori, S. J. Y. (2010). Conjunctive encoding of movement and reward by ventral tegmental area neurons in the freely navigating rodent. *Behav. Neurosci.* 124, 234–247. doi:10.1037/a0018865

Puryear, C. B., King, M., and Mizumori, S. J. Y. (2006). Specific changes in hippocampal spatial codes predict spatial working memory performance. *Behav. Brain Res.* 169, 168–175. doi:10.1016/j.bbr.2005.12.007

Ranck, J. B. Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. *Exp. Neurol.* 41, 461–531. doi:10.1016/0014-4886(73)90290-2

Robinson, T. E., and Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* 47(Suppl. 1), 33–46. doi:10.1016/j.neuropharm.2004.06.025

Sabatino, M., Ferraro, G., Liberti, G., Vella, N., and La Grutta, V. (1985). Striatal and septal influence on hippocampal theta and spikes in the cat. *Neurosci. Lett.* 61, 55–59. doi:10.1016/0304-3940(85)90400-8

Samsonovich, A., and McNaughton, B. L. (1997). Path integration and cognitive mapping in a continuous attractor neural network model. *J. Neurosci.* 17, 5900–5920.

Save, E., Buhot, M. C., Foreman, N., and Thinus-Blanc, C. (1992a). Exploratory activity and response to a spatial change in rats with hippocampal or posterior parietal cortical lesions. *Behav. Brain Res.* 47, 113–127. doi:10.1016/S0166-4328(05)80118-4

Save, E., Poucet, B., Foreman, N., and Buhot, M. C. (1992b). Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. *Behav. Neurosci.* 106, 447–456. doi:10.1037/0735-7044.106.3.447

Save, E., Nerad, L., and Poucet, B. (2000). Contribution of multiple sensory information to place field stability in hippocampal place cells. *Hippocampus* 10, 64–76. doi:10.1002/(SICI)1098-1063(2000)10:1<64::AID-HIPO7>3.0.CO;2-Y

Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science* 275, 1593–1599. doi:10.1126/science.275.5306.1593

Shetty, P. K., Galeffi, F., and Turner, D. A. (2012). Cellular links between neuronal activity and energy homeostasis. *Front. Pharmacol.* 3:1–14. doi:10.3389/fphar.2012.00043

Siapas, A. G., Lubenov, E. V., and Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46, 141–151. doi:10.1016/j.neuron.2005.02.028

Smith, D. M., and Mizumori, S. J. (2006a). Hippocampal place cells, context, and episodic memory. *Hippocampus* 16, 716–729. doi:10.1002/hipo.20208

Smith, D. M., and Mizumori, S. J. (2006b). Learning-related development of context-specific neuronal responses to places and events: the hippocampal role in context processing. *J. Neurosci.* 26, 3154–3163. doi:10.1523/JNEUROSCI.3234-05.2006

Smith, D. M., Wakeman, D., Patel, J., and Gabriel, M. (2004). Fornix lesions impair context-related cingulothalamic neuronal patterns and concurrent discrimination learning. *Behav. Neurosci.* 118, 1225–1239. doi:10.1037/0735-7044.118.6.1225

Tabuchi, E. T., Mulder, A. B., and Wiener, S. I. (2000). Position and behavioral modulation of synchronization of hippocampal and accumbens neuronal discharges in freely moving rats. *Hippocampus* 10, 717–728. doi:10.1002/1098-1063(2000)10:6<717::AID-HIPO1009>3.0.CO;2-3

Tanila, H., Shapiro, M. K., and Eichenbaum, H. (1997). Discordance of spatial representation in ensembles of hippocampal place cells. *Hippocampus* 7, 613–623. doi:10.1002/(SICI)1098-1063(1997)7:6<613::AID-HIPO4>3.3.CO;2-#

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., et al. (2007). Schemas and memory consolidation. *Science* 316, 76–82. doi:10.1126/science.1135935

Tulving, E. (2002). Episodic memory: from mind to brain. *Ann. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Turrigiano, G. G. (1999). Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. *Trends Neurosci.* 22, 221–227. doi:10.1016/S0166-2236(98)01341-1

Turrigiano, G. G. (2008). The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 135, 422–435. doi:10.1016/j.cell.2008.10.008

Turrigiano, G. G. (2011). Homeostatic synaptic plasticity: Local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb. Perspect. Biol.* 4, a005736. doi:10.1101/cshperspect.a005736

Turrigiano, G. G., Leslie, K. R., Desai, N. S., Rutherford, L. C., and Nelson, S. B. (1998). Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391, 892–896. doi:10.1038/36103

Turrigiano, G. G., and Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nat. Rev. Neurosci* 5, 97–107. doi:10.1038/nrn1327

van der Meer, M. A., and Redish, A. D. (2009). Low and high gamma oscillations in rat ventral striatum have distinct relationships to behavior, reward, and spiking activity on a learned spatial decision task. *Front. Integr. Neurosci.* 3:9. doi:10.3389/neuro.07.009.2009

Vanderwolf, C. H. (1969). Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* 26, 407–418. doi:10.1016/0013-4694(69)90092-3

Varela, F., Lachaux, J. P., Rodriguez, E., and Martinerie, J. (2001). The brain web: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* 2, 229–239. doi:10.1038/35067550

Vida, I., Bartos, M., and Jonas, P. (2006). Shunting inhibition improves robustness of gamma oscillations in hippocampal interneuron networks by homogenizing firing rates. *Neuron* 49, 107–117. doi:10.1016/j.neuron.2005.11.036

Vinogradova, O. S. (1995). Expression, control, and probably functional significance of the neuronal theta-rhythm. *Prog. Neurobiol.* 45, 523–583. doi:10.1016/0301-0082(94)00051-I

Whittington, M. A., Traub, R. D., and Jefferys, J. G. (1995). Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 373, 612–615. doi:10.1038/373612a0

Wiener, S. I. (1996). Spatial, behavioral and sensory correlates of hippocampal CA1 complex spike cell activity: implications for information processing functions. *Prog. Neurobiol.* 49, 335–361. doi:10.1016/0301-0082(96)00019-6

Wikenheiser, A. M., and Redish, A. D. (2011). Changes in reward contingency modulate the trial-to-trial variability of hippocampal place cells. *J. Neurophysiol.* 106, 589–598. doi:10.1152/jn.00091.2011

Womelsdorf, T., Fries, P., Mitra, P. P., and Desimone, R. (2006). Gamma-band synchronization in visual cortex predicts speed of change detection. *Nature* 439, 733–736. doi:10.1038/nature04258

Womelsdorf, T., Schoffelen, J. M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., et al. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612. doi:10.1126/science.1139597

Wood, E. R., Dudchenko, P. A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neural activity. *Nature* 397, 613–616. doi:10.1038/17605

Wood, E. R., Dudchenko, P. A., Robitsek, R. J., and Eichenbaum, H. (2000). Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27, 623–633. doi:10.1016/S0896-6273(00)00071-4

Yeshenko, O., Guazzelli, A., and Mizumori, S. J. (2004). Context-dependent reorganization of spatial and movement representations by simultaneously recorded hippocampal and striatal neurons during performance of allocentric and egocentric tasks. *Behav. Neurosci.* 118, 751–769. doi:10.1037/0735-7044.118.4.751

Young, B. J., Fox, G. D., and Eichenbaum, H. (1994). Correlates of hippocampal complex-spike cell activity in rats performing a nonspatial radial maze task. *J. Neurosci.* 14, 6553–6563.

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Hippocampal signatures of episodic memory: evidence from single-unit recording studies

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What hippocampal neural firing patterns signal memory and, more importantly, how is this memory code used by associated structures to translate a memory into a decision or action? Candidate hippocampal activity patterns will be discussed including (1) trajectory-specific firing of place cells with place fields on an overlapping segment of two (or more) distinct trajectories (2) prospective firing of hippocampal neurons that signal an upcoming event or action, and (3) place cell remapping to changes in environment and task. To date, there has not been compelling evidence for any of these activity patterns being the neural substrate of episodic memory. New findings suggest that learning and memory processes are emergent properties of interregional interactions and not localized within any one discrete brain region. Therefore, the next step in understanding how remapping and trajectory coding participate in memory coding may be to investigate how these activity patterns relate to activity in anatomically connected structures such as the prefrontal cortex.

Keywords: place cell remapping, trajectory coding, hippocampal-prefrontal synchrony, electrophysiology, dorsal hippocampus

INTRODUCTION

For decades scientists have been attempting to understand how memories are made, stored, and retrieved in the brain. Unraveling this problem is not only fascinating in its own right, but can lead to the development of treatments for a multitude of disorders and conditions that affect the ability to form and use memories in our day-to-day experiences. In recent years, the development of large-scale neural recording techniques has advanced our knowledge of neural underpinnings behind memory formation and retrieval. However, a challenge that remains in the field is the large degree of uncertainty in linking neural firing patterns with complex cognitive operations. For that reason, despite the many investigations of the neural correlates of memory, much ambiguity remains regarding which brain structures are involved and the nature of their involvement. An extensive body of literature has established the hippocampus as a critical brain structure in episodic memory. Hippocampal lesions (or disruption of hippocampal inputs) lead to performance impairments in tasks that rely on the encoding and retrieval of specific trajectories through a familiar environment. These tasks include the delayed spatial alternation task (Rawlins and Olton, 1982; Brito et al., 1983; Stanton et al., 1984; Aggleton et al., 1995; Czerniawski et al., 2009), the eight-arm radial maze (Olton et al., 1979), and the Morris water maze (Eichenbaum et al., 1990). Recording studies, in turn, are beginning to uncover the exact mechanisms utilized by the hippocampus to accomplish memory processing. The most direct way to study cellular mechanisms that support episodic memory is to record from populations of neurons while animals perform memory tasks. Candidate neural activity patterns that have been linked to episodic memory will be discussed in this review including (1) trajectory-specific firing of place cells with place fields on an overlapping segment of two (or more) distinct trajectories (2) prospective firing of hippocampal neurons (3) place cell remapping to changes in environment and task. Though these phenomena may indeed serve as a neural substrate for episodic memory, a complex process like episodic memory most likely relies on functional interactions among a network of brain regions. Therefore, developing an understanding of these hippocampal activity patterns in the broader context of network interactions could be a critical step in identifying the neural correlates of memory.

HIPPOCAMPAL INVOLVEMENT IN WORKING MEMORY AND SPATIAL COGNITION

Spatial working memory tasks have been an essential tool for developing rodent models of memory. However, during these tasks, there are presumably several processes at work: working memory, the temporary storage of information that is necessary for complex cognitive processes (Baddeley, 1992); spatial cognition, the development and use of a "cognitive map" of the environment (O'Keefe and Nadel, 1978) and episodic encoding and retrieval of specific trajectories through the environment (Hasselmo, 2009). In a typical working memory task, the spatial alternation task, rats are placed on an elevated T-maze and required to alternate between the left and right goal arms on each trial. The task relies on the rat's ability to remember which goal arm was visited on the previous trial in order to correctly select the opposite goal arm. There are two main versions of this task: continuous alternation, in which the rat alternatively visits the left and right goal arms in a "figure 8" pattern, and delayed alternation, in which the rat also alternates visits to the left and right goal arm, but pauses in the start box between trials. Because the insertion of the delay period necessitates remembrance of the previously rewarded goal location, the

memory demand is theoretically greater for delayed version of the alternation task than for the continuous version. Accordingly, hippocampal lesions (or disruption of its inputs) lead to performance impairments in delayed alternation (Rawlins and Olton, 1982; Brito et al., 1983; Stanton et al., 1984; Ainge et al., 2007a; Czerniawski et al., 2009), but not continuous alternation (Ainge et al., 2007a). Although these studies have elucidated the brain regions that are necessary for memory, it is unclear if the results can be extrapolated to episodic memory in humans. In fact, episodic memory has been explicitly defined as having a "what" component, a "when" component, and a "where" component and as a process that is not present in animals other than humans (Tulving and Markowitsch, 1998). However, there is strong evidence that episodic memory is not a uniquely human phenomenon. Clayton and Dickinson (1999) have demonstrated that Western scrub jays can remember not only where a food cache was stored, but what type of food it was and how long ago it was cached. The type of memory that includes spatial, temporal information is often called "episodic-like" memory when applied to experimental animals. Fortin et al. (2002) demonstrated that "episodic-like" memory depends on the hippocampus by showing that rats with hippocampal lesions were unable to perform a sequential odor task. Rats were presented with a sequence of five odors and after a 3-min delay were presented with two of the odors and were required to identify which was presented earlier in the sequence. Rats with hippocampal lesions were impaired on this task, but importantly were not impaired on a probe recognition task in which they were required to discriminate between novel and familiar odors. Although this study demonstrated that rats could form hippocampus-dependent "what–when" representations, the "where" component was missing. Subsequent studies showed that rats (Ergorul and Eichenbaum, 2004) and mice (DeVito and Eichenbaum, 2010) were significantly impaired on tasks that required the integration of "what," "when," and "where" information following hippocampal damage. Together, these lesion studies have established the hippocampus as a critical brain region in many types of memory, including episodic memory. In order to examine the physiological properties that give rise to episodic memory, we must turn to studies that have recorded populations of hippocampal neurons in freely moving rats.

SPATIAL CODING IN HIPPOCAMPAL NEURONS

Hippocampal neurons known as place cells code spatial location by showing selective elevations in firing rate when the rat occupies specific locations in an environment (O'Keefe and Nadel, 1978). Although the discovery of hippocampal place cells was a significant advancement in the understanding of hippocampal physiology, it has been difficult to reconcile the human clinical findings that the hippocampus was critical for (non-spatial) episodic memory relative to the rodent findings, which suggested that the hippocampus was a "cognitive map" of the environment and thus participated solely in spatial processing. Additional research soon revealed that current spatial location was not the only factor that modified the behavior of place cells. McNaughton et al. (1983) found that the firing rate of a given place cell could be influenced by the direction in which a rat was heading when the rat passed through the neuron's place field. This place cell "directionality" was observed when rats moved through a radial arm maze, such that a given place cell would show a significantly different firing rate when the rat was headed toward the end of an arm (outbound journeys) than when the rat was headed toward the center of the maze (inbound journeys), and vice versa. This within-field directional coding provided early evidence that principal cells in the hippocampus could respond to an animal's previous and upcoming location in addition to its current location in an environment. However, place cell directionality only appeared under certain experimental conditions. When rats foraged for food in a circular or square open-field enclosure, the firing rates of place cells did not differ significantly as a function of the future or past position of the animal (Breese et al., 1989; Muller et al., 1994). Place cell directionality was again seen when rats performed a spatial navigation task in a radial arm maze, but not when rats performed a non-spatial odor discrimination task (Wiener et al., 1989). These results suggested that directional coding in the hippocampus only appears when an animal moves through a place field in a stereotyped manner, such as when an animal's trajectory through a place field is limited by the experimental apparatus in which testing is taking place.

Could the physical boundaries of an environment be the sole factor in determining whether place cell firing could be modified by an animal's direction? Markus et al. (1995) first recorded place cells while rats navigated through a radial arm maze, and then recorded place cells as rats foraged in an open cylinder. Predictably, the experimenters found that directional coding of place cells was observed in the radial arm maze, but not the open cylinder. However, when the task contingency in the open cylinder was altered so that the animals no longer foraged for randomly distributed food rewards, but were taught to run to the periphery of the cylinder toward reward zones that were sequentially baited, place cells began to display the same directionally modified properties that were observed in the radial arm maze. Thus, directional coding could be influenced by task strategy, even when the task was performed in an open-field environment.

PLACE CELL REMAPPING

Place cells are known to exhibit radical changes in firing properties with sometimes subtle changes in the features of an environment, a property known as "remapping" (for review Muller et al., 1996; Colgin et al., 2008). Operationally, remapping is defined as a change in firing rate and/or place field location in the "new" environment. These changes can manifest themselves in a number of ways: A place cell that ceases to fire; a previously silent place cell that begins to fire; or a place field that shifts to an entirely new location within the environment. The first demonstration of remapping was shown in a study by Muller and Kubie (1987). It was found that doubling the area of a circular or square enclosure caused a subset of place cells to remap. Similarly, in this same study, a population of hippocampal neurons was recorded while rats foraged in both circular and square environments. There was no relationship between the firing field locations in one enclosure and the field location in the other enclosure, suggesting that the hippocampal ensemble had a separate representation for each environment. Following this initial demonstration, Bostock et al. (1991) used a black or white cue card as a polarizing cue in an otherwise-identical recording chamber. The first time that the

black card was replaced by the white card, few place cells changed. But, after alternating between the two cards several times, the place cells began to discriminate between the two "environments," with some cells shifting their place field location, some ceasing to fire in one environment and some showing "complex" or "global" remapping: changing in both location and shape. It was hypothesized that remapping allowed the rat to disambiguate similar environments; reducing interference by having populations of hippocampal neurons alter their firing correlates between conditions. This demonstration of remapping after experience with an environment was also seen in investigations of remapping between circular and square enclosures. Lever et al. (2002) recorded the same neurons in two separate enclosures that differed only in shape of the exterior walls: circular or square. As in the Bostock study, the first exposure to the changed environment did not induce a change in the place field locations or shape. However, the neurons began to discriminate between environments after multiple switches. Wills et al. (2005) morphed the recording enclosure gradually from a square to a circle in order to investigate further how hippocampal neurons differentiate between circular and square enclosures. Most hippocampal neurons showed remapping and the remapping was abrupt and consistent across simultaneously recorded cells, suggesting that the hippocampal network codes changes in the environment in a coherent manner. Importantly, it is not only sensory changes in the environment that can induce remapping. As described above, Markus et al. (1995) found that requiring the rat to switch from a foraging strategy to a goal-directed strategy in the same enclosure induced remapping. Similarly, Moita et al. (2004) showed remapping based on whether fear conditioning was performed in the environment.

Recent studies have shown place cell remapping in response to changes in task (in the absence of changes in the spatial layout of the environment). Ferbinteanu et al. (2011) showed that switching from a cue-guided strategy to a spatial strategy prompted place cell remapping. Importantly, the overt behavior of the rat was the same in the two different tasks; only the memory demand differed. Ainge et al. (2012) compared prospective coding across behaviorally identical tasks and showed no differences in the coding behavior of hippocampal neurons between the memory-guided and cue-guided conditions. Conversely, a recent study showed that a large percentage of hippocampal neurons remapped between continuous alternation and conditional discrimination tasks, a phenomenon that was termed "task remapping" (See **Figure 1**; Hallock and Griffin, 2013). When a delay was added to the alternation task, however, there was very little remapping between tasks, suggesting that the temporal structure of the task (discrete vs. continuous trials) was driving the place cell remapping rather than the memory demand of the task (Hallock and Griffin, 2013).

At this point, it is important to distinguish between the two types of remapping seen in hippocampal neural populations. Rate remapping, defined as a significant difference in place field firing rate without a change in place field location, was first reported in response to "local" changes in an environment: changing the wall color or shape of the recording enclosure within the same room (Leutgeb et al., 2005). In contrast, global remapping, defined as changes in place field locations and firing rate, is induced by either physically moving the rat between recording rooms as in Leutgeb et al. (2005) or by changing the recording environment substantially (e.g., Wills et al., 2005). Rate remapping theoretically allows the hippocampus to code different experiences that occur in the same location, whereas global remapping allows similar experiences to be distinguished based on where the experience took place (Leutgeb et al., 2005). The findings showing that place cells do not exclusively code spatial location have led many to speculate that remapping could be a mechanism for linking a spatial location (the "where") to events (the "what" and the "when") occurring in that location (Colgin et al., 2008). Formation of this "what-when-where" representation is a critical component of episodic memory.

TRAJECTORY CODING IN HIPPOCAMPAL NEURONS

Evidence for directional coding and remapping in the hippocampus added another chapter to the cognitive mapping theory of hippocampal function. Place cells could be tied to the current, past, or future spatial location. Directionally dependent firing in the hippocampus also added a possible clue of how hippocampal neurons participated in the formation, storage, and retrieval of contextually unique events that comprise episodic memories. Similar to the argument that place cell remapping could be a mechanism for linking the "where" with the "what" and the "when," the reasoning was that if place fields are present in one situation (e.g., the rat is moving in a particular direction) and absent in another situation, the neurons cannot exclusively be coding spatial location (Wood et al., 2000). It was tempting to speculate that the neurons could be coding memory on top of a place code. Since the pioneering studies on the amnesic patient H.M., who had undergone a surgical procedure to remove large portions of his medial temporal lobe in order to control seizure activity, it had been known that the hippocampus was critical for the formation of new episodic memories (Scoville and Milner, 1957). However, evidence from single-unit recording of hippocampal neurons in animals suggested that the primary role of the hippocampus was spatial processing (O'Keefe and Nadel, 1978). Although spatial mapping and episodic memory are not mutually exclusive, there are many aspects of memory that are non-spatial. Using a continuous non-matching to sample odor task, Wood et al. (1999) found that the majority of recorded hippocampal neurons (∼85%) coded for non-spatial variables such as odor, trial type (match vs. non-match), approaching the stimulus cup, or a conjunctive coding of these non-spatial variables with location. These findings suggested that the hippocampus represents both spatial and non-spatial information related to memory. Subsequent studies by Frank et al. (2000) and Wood et al. (2000) began to tease apart the cognitive mapping and episodic memory functions of the hippocampus by recording from hippocampal neurons during tasks in which an animal was required to remember a previously visited location in order to successfully retrieve a reward on an upcoming trial. Wood et al. (2000) showed that when rats ran a continuous spatial alternation task in a T-maze, the majority of neurons with place fields on the stem of the maze showed a significantly higher firing rate during either left- or right-turn trials. Frank et al. (2000) added to this line of research by showing that place cell firing rate could be tied to both past and future location by recording

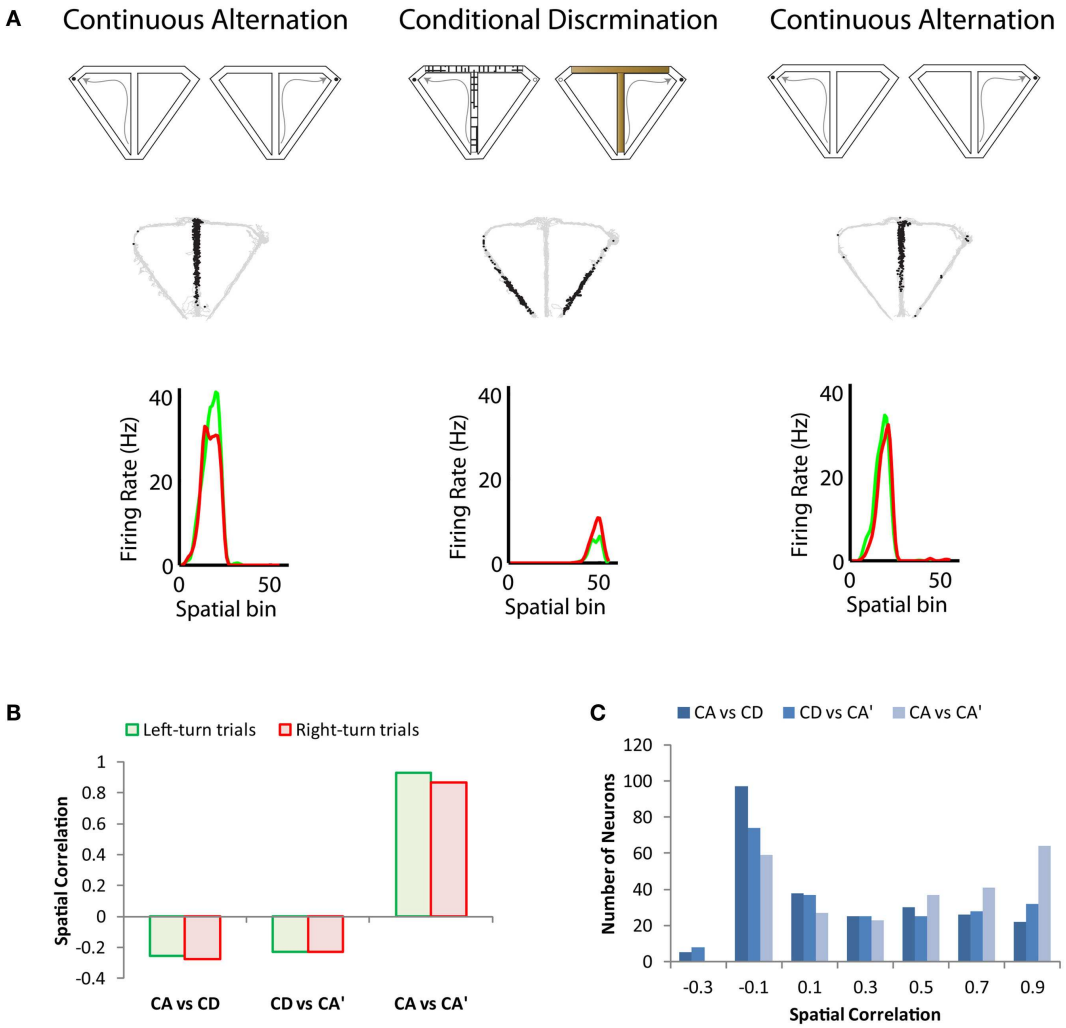


FIGURE 1 | Illustration of task remapping exhibited by dorsal CA1 hippocampal neurons. **(A)** The top panel is a schematic of the continuous alternation and conditional discrimination tasks. Rats were trained on both tasks prior to implantation of recording microdrives. Recoding sessions consisted of a set of continuous alternation trials, followed by a set of conditional discrimination trials, followed by a second set of continuous alternation trials. The middle panel shows the trajectory of the rat (gray) with superimposed spike locations (black) during the first set of continuous alternation trials (CA, left), a set of conditional discrimination trials (CD, middle), and second set of continuous alternation trials (CA', right). The neuron has a prominent place field on the central stem of the T-maze during both sets of continuous alternation trials, which remaps to the return arms of the T-maze during the set of conditional discrimination trials. The bottom panel shows the average firing rate for left (green) and right (red) trials across 5-cm spatial bins of the T-maze. Spatial bins 1–24 correspond to the central stem region of the maze; 25–26 to the choice point; 27–36 to the goal arm; and 37–55 to the return arm. The neuron does not exhibit trajectory coding as shown by the similar firing rate distributions on left- and right-turn trials. **(B)** Spatial correlation of bin firing rates across the continuous alternation and conditional discrimination tasks for the neuron shown in **(A)**. The spatial correlation is low between the conditional discrimination task and both sets of continuous alteration trials (CA vs. CD and CD vs. CA'), which indicates strong remapping. Conversely, the spatial correlation is high between the two sets of continuous alternation trials (CA vs. CA'). **(C)** Spatial correlation values across tasks for a population of recorded dorsal CA1 neurons. The population showed the same task remapping pattern as the neuron in **(A)**: high correlation values between sets of continuous alternation trials and low correlation values across the conditional discrimination and continuous alternation tasks. Data adapted from Hallock and Griffin (2013).

in a W-maze as rats alternated between the two outside arms via the central arm. This study revealed that firing rate was modulated both during inbound journeys through the central arm (indicative of retrospective coding), and outbound journeys (indicative of prospective coding).

Providing further evidence that hippocampal neurons could flexibly code for both future and past position, Ferbinteanu and Shapiro (2003) recorded from dorsal hippocampus while rats performed a spatial memory task in a plus maze, in which starting location and goal location could be varied. Neuronal firing rate

was heavily modified by the trajectory of an animal, with neurons that fired on a start arm selectively signaling journeys to a specific goal arm, and neurons that fired on a goal arm selectively signaling journeys from a specific start arm. Hippocampal neurons display similar trajectory-dependent coding in a maze that has multiple choice points within a journey, as shown during recordings on a concatenated Y-maze (Ainge et al., 2007b). When a delay period is introduced between trials of the T-maze continuous alternation task, neurons cease to show trajectory-specific coding on the maze stem. Instead, neurons that fire during the delay period show firing rates that are modulated by the past or future location of the animal, indicating that trial-specific activity takes place at the location where memory coding that is necessary for contextual disambiguation is most likely to happen (Ainge et al., 2007a; Pastalkova et al., 2008). It has been theorized that this type of trajectory coding is a neural mechanism for memory processing, as hippocampal neurons can fire at different rates in a common location as a function of the animal's future or past position, and thus separate distinct events that occur in common spatial locations (Hasselmo and Eichenbaum, 2005; Smith and Mizumori, 2006; Griffin et al., 2007).

However, evidence from other experiments has challenged the idea that trajectory coding is important for distinguishing between events that contain common features. In one study, trajectory coding was not found as rats alternated continuously between arms of a Y-maze (Lenck-Santini et al., 2001). When rats are running on a circular track, trajectory coding is seen in larger proportion when local cues are present, indicating that levels of sensory input can influence bidirectional coding (Battaglia et al., 2004). Bower et al. (2005) showed that trajectory coding was not necessary for the successful performance of a task in which rats had to disambiguate between journeys that contained repeating elements that were common between different trajectories. Interestingly, trajectory coding did appear in this study, but only under certain circumstances; specifically, when removable barriers were introduced during training, and when rewards were withheld at intermediate steps and only given at the end of a trajectory. Further challenging the notion that trajectory coding is a hippocampal-dependent memory signal, trajectory coding appears in tasks that are not dependent on the integrity of the hippocampus (Wood et al., 2000; Lee et al., 2006; Ferbinteanu et al., 2011; Griffin et al., 2012). Trajectory coding is seen in equal proportion during a spatial task on a plus maze that is hippocampus-dependent, and a cue-approach task on a plus maze that is not hippocampus-dependent (Ferbinteanu et al., 2011). Trajectory coding is seen in a large proportion of hippocampal neurons during the continuous alternation task, which is not dependent on the functional integrity of the hippocampus (Wood et al., 2000; Lee et al., 2006; Griffin et al., 2012). Other studies have found that trajectory coding is not seen during a cue-approach task in a radial arm maze (Berke et al., 2009) and conditional discrimination tasks in T-mazes (Ainge et al., 2012; Griffin et al., 2012). These mixed results indicate that trajectory coding is not simply a mechanism for context-specific encoding in episodic memory, but is rather a complex phenomenon that is influenced by a variety of sensory and behavioral components of experiences.

More recent studies have begun to unravel the links between experience and trajectory coding by manipulating task, duration of exposure, and visual cues surrounding the recording environment. When rats switch from a well-known task strategy to a novel strategy in a W-maze, retrospective coding is seen before rats reach performance levels above chance on the novel task (Ji and Wilson, 2008). In agreement with this finding, Bahar and Shapiro (2012) found that when the goal arm was switched during a well-learned spatial task in a plus maze, prospective and retrospective trajectory coding stayed consistent even when animals were not yet able to perform the new variation of the task. In contrast, when the arrangement of visual cues in the recording room was significantly altered, trajectory coding disappeared and only returned when rats had oriented to the new environmental layout. Upon introduction to a circular track, hippocampal neurons show little directionally dependent variation in firing rate; as rats gain more experience on the track, trajectory coding develops over time (Navratilova et al., 2012). Finally, when rats are trained on both continuous alternation and conditional discrimination in a T-maze, trajectory coding on the maze stem is virtually absent when the rat switches between the two tasks, indicating that experience during task training has a large influence on whether or not trajectory coding will be observed (Hallock and Griffin, 2013). In this same study, prospective trajectory coding was seen when rats switched between delayed alternation and conditional discrimination tasks on the same T-maze. This prospective coding was only observed during the delay period of the delayed alternation task, suggesting that when a delay period is introduced that increases the hippocampal-dependent memory demand of a task, hippocampal neurons may be more likely to display trajectory coding, even when previous training experience would not otherwise favor its development.

The initial discovery that the firing rate of place cells was influenced by the rats' specific trajectory and thus by recent experiences led to speculation that this firing rate difference could be a "rate code" for episodic memory. However, this notion was challenged by the finding that trajectory coding was rarely observed in hippocampus-dependent tasks. After over a decade of research, the debate over whether trajectory coding represents a hippocampal memory signal or perhaps a broader phenomenon that encompasses training history and the structure of the task has not been resolved. More experiments will need to be completed in order to delineate the determining factors that produce trajectory coding during different tasks in different environments. It is clear, however, that both trajectory coding and remapping reflect coding mechanisms for distinguishing between tasks and environments. Remapping tends to occur with changes to the recording environment or task and trajectory coding is a specific type of remapping that occurs within a task when there are continuously overlapping paths toward different goal locations. In order to gain a true appreciation for the content of the information processed by the hippocampus, it may be fruitful to look outside of the hippocampus proper and explore the manner in which the contextual information is communicated to anatomically connected structures.

HIPPOCAMPAL–PREFRONTAL INTERACTIONS DURING MEMORY PROCESSING

Emerging evidence suggests that the neural signature of complex cognitive functions may not reside within an individual brain structure, but in the dynamic interactions that take place within system of related structures. Consistent with this notion, a functional imaging study in humans demonstrated selective activation of both the hippocampus and PFC during a memory task (Stern et al., 2001). The interactions between hippocampus and prefrontal cortex are of particular interest because (1) these structures have been shown to be coactive during memory tasks; (2) there are direct and indirect anatomical connections between them and (3) there is emerging evidence for hippocampal–prefrontal interactions during simple cognitive tasks. Disruption of hippocampus–mPFC interactions may result in failed transfer of spatial and contextual information processed by the hippocampus to the circuitry in mPFC responsible for decision making and goal-directed behavior (Colgin, 2011; Gordon, 2011). The mPFC is known to receive direct monosynaptic glutamatergic input from CA1 and subiculum of hippocampal formation (Ferino et al., 1987; Jay and Witter, 1991; Jay et al., 1992). From this pattern of connections, it is tempting to conclude that the functional interactions between the hippocampus and prefrontal cortex are an important component of complex behavior. Despite many demonstrations of individual contributions of hippocampus and mPFC to memory-guided behavior, the interactions between these two brain regions during complex tasks has not yet been well studied. One way to directly observe a functional interaction is to measure oscillatory synchrony, changes in activity patterns within a specific frequency range that occur simultaneously in disparate brain regions. Two measures of synchrony are *coherence*, a measure that reflects the strength of the temporal relationship between two oscillations and *entrainment*, a measure of the consistency with which action potentials from a neuron in one region occur on a particular phase of an oscillation in another region. In general, theta synchrony appears to be a mechanism used by the hippocampus to convey information to anatomically connected structures, including the mPFC (Siapas and Wilson, 1998; Hyman et al., 2005; Jones and Wilson, 2005; Siapas et al., 2005; Benchenane et al., 2010), as well as the amygdala (Seidenbecher et al., 2003; Popa et al., 2010) and the striatum (Berke et al., 2004; Tort et al., 2008). Hippocampal theta is one of the few sustained oscillations in the brain. It is a ∼8 Hz oscillation dominating the hippocampal local field potential during exploration in the rodent (Buzsáki, 2002). Slow oscillations like the hippocampal theta rhythm are well-suited to coordinate interactions between disparate brain regions because the length of the theta cycle is sufficient to accommodate long conduction delays and even polysynaptic interactions. mPFC neurons exhibit strong entrainment to the hippocampal theta rhythm during exploration (Siapas and Wilson, 1998; Hyman et al., 2005) and spatial working memory (Jones and Wilson, 2005; Hyman et al., 2010;), suggesting a functional interaction between hippocampus and mPFC that may be especially important in situations in which demands on working memory are high. A recent study examined hippocampal–prefrontal interactions by performing lesions of the hippocampus and recording from mPFC neurons during a conditioned place preference task in which rats were required to wait in a goal zone before receiving food reward (Burton et al., 2009). Single mPFC neurons showed anticipatory activity during the wait time in the goal zone. Importantly, this activity was diminished in hippocampal-lesioned rats and this disruption was accompanied by impairments in task performance. This anticipatory activity may represent the expectation of forthcoming events. The disruption of this activity in hippocampal-lesioned rats suggests that hippocampal input may provide the mPFC with contextual information that is necessary for the selection of appropriate responses. A crucial next step in this line of research is to examine the link between trajectory coding, remapping, and hippocampal-prefrontal synchrony. It is reasonable to predict that hippocampal neurons that exhibit trajectory coding or remapping would be preferentially entrained to prefrontal activity when memory demand is high, confirming that the neural activity patterns that encode memories encompass a network of interconnected brain regions. Finally, the only way to address the issue of whether there is a causal link between neurophysiological phenomena and memory is to use multiple technical approaches. Therefore, a future direction in the area of memory research should be to combine techniques that measure neural activity patterns such as neurophysiology with inactivation techniques such as pharmacological inactivation of discrete brain regions (e.g., Brandon et al., 2011). The question of whether trajectory coding and remapping persist after disruption of the hippocampal-prefrontal circuit remains an open question.

CONCLUSION

Hippocampal place cell remapping has been demonstrated most commonly in open-field environments. In these environments, the rats are not required to perform any specific task to obtain food reward, but instead must forage for food pellets scattered across the floor. The fact that place cell remapping can be driven not only by changes in the layout of an environment, but also by experiences within that environment suggests that remapping could play a key role in the formation of an episodic memory by linking the "what" and the "when" with the "where." However, because studies that have reported global remapping have manipulated the sensory environment, the evidence so far suggests that remapping is the code for a context change; not an episode within that context. Rate remapping is more often associated with episodic memory in the literature. However, the evidence is simply insufficient at the stage to make statements about its role in episodic memory.

A number of investigations have recorded hippocampal neurons during memory task performance in apparatuses that restrict the rats' movement to a path or trajectory. These tasks include spatial alternation (both delayed and continuous), serial reversals, delayed non-match to position/place, complex sequence tasks, and visuospatial conditional discrimination. Reminiscent of the changes seen in place cell firing properties in response to sensory or cognitive information, some, but not all, of these studies have found that hippocampal neurons code specific trajectories. The most robust demonstrations of trajectory coding have been seen in continuous spatial alternation (Wood et al., 2000; Lee et al., 2006) and serial reversal tasks (Ferbinteanu and Shapiro, 2003).

Interestingly, some tasks that are known to depend on the hippocampus, such as delayed spatial alternation do not elicit robust trajectory coding (Ainge et al., 2007a; Griffin et al., 2012; Hallock and Griffin, 2013). This set of findings argues against the interpretation of trajectory coding being a memory signal used in task performance. Instead, trajectory coding may be a special case of remapping, in which the hippocampal network alternates between representing two or more different trajectories. The next step in understanding how remapping and trajectory coding participate in memory coding may be to look outside of the hippocampus in downstream structures such as the mPFC. By investigating mPFC–hippocampal interactions and synchrony during memory task performance and, most importantly, relating these interactions to trajectory coding and remapping of hippocampal neurons, we may finally uncover the meaning of these striking hippocampal firing patterns.

REFERENCES

Aggleton, J. P., Neave, N., Nagle, S., and Hunt, P. R. (1995). A comparison of the effects of anterior thatlamic, mamillary body and fornix lesions on reinforced spatial alternation. *Behav. Brain Res.* 68, 91–101. doi:10.1016/0166-4328(94)00163-A

Ainge, J. A., van der Meer, M. A. A., Langston, R. F., and Wood, E. R. (2007a). Exploring the role of context-dependent hippocampal activity in spatial alternation behavior. *Hippocampus* 17, 988–1002. doi:10.1002/hipo.20301

Ainge, J. A., Tamosiunaite, M., Woergoetter, F., and Dudchenko, P. A. (2007b). Hippocampal CA1 place cells encode intended destination on a maze with multiple choice points. *J. Neurosci.* 27, 9769–9779. doi:10.1523/JNEUROSCI.2011-07.2007

Ainge, J. A., Tamosiunaite, M., Worgotter, F., and Dudchenko, P. A. (2012). Hippocampal place cells encode intended destination, and not a discriminative stimulus, in a conditional T-maze task. *Hippocampus* 22, 534–543. doi:10.1002/hipo.20919

Baddeley, A. (1992). Working memory. *Science* 255, 556–559. doi:10.1126/science.1736359

Bahar, A. S., and Shapiro, M. L. (2012). Remembering to learn: independent place and journey coding mechanisms contribute to memory transfer. *J. Neurosci.* 32, 2191–2203. doi:10.1523/JNEUROSCI.3998-11.2012

Battaglia, F. P., Sutherland, G. R., and McNaughton, B. L. (2004). Local sensory cues and place cell directionality: additional evidence of prospective coding in the hippocampus. *J. Neurosci.* 24, 4541–4550. doi:10.1523/JNEUROSCI.4896-03.2004

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., et al. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron* 66, 921–936. doi:10.1016/j.neuron.2010.05.013

Berke, J. D., Breck, J. T., and Eichenbaum, H. (2009). Striatal versus hippocampal representations during win-stay maze performance. *J. Neurophysiol.* 101, 1575–1587. doi:10.1152/jn.91106.2008

Berke, J. D., Okatan, M., Skurski, J., and Eichenbaum, H. B. (2004). Oscillatory entrainment of striatal neurons in freely moving rats. *Neuron* 436, 883–896. doi:10.1016/j.neuron.2004.08.035

Bostock, E., Muller, R. U., and Kubie, J. L. (1991). Experience-dependent modifications of hippocampal place cell firing. *Hippocampus* 1, 193–205. doi:10.1002/hipo.450010207

Bower, M. R., Euston, D. R., and McNaughton, B. L. (2005). Sequential-context-dependent hippocampal activity is not necessary to learn sequences with repeated elements. *J. Neurosci.* 25, 1313–1323. doi:10.1523/JNEUROSCI.2901-04.2005

Brandon, M. P., Bogaard, A. R., Libby, C. P., Connerney, M. A., Gupta, K., and Hasselmo, M. E. (2011). Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science* 332, 595–599. doi:10.1126/science.1201652

Breese, C. R., Hampson, R. E., and Deadwyler, S. A. (1989). Hippocampal place cells: stereotypy and plasticity. *J. Neurosci.* 9, 1097–1111.

Brito, G. N., Davis, B. J., Stopp, L. C., and Stanton, M. E. (1983). Memory and the septo-hippocampal cholinergic system in the rat. *Psychopharmacology (Berl.)* 81, 315–320. doi:10.1007/BF00427569

Burton, B. G., Hok, V., Save, E., and Poucet, B. (2009). Lesion of the ventral and intermediate hippocampus abolishes anticipatory activity in the medial prefrontal cortex of the rat. *Behav. Brain Res.* 199, 222–234. doi:10.1016/j.bbr.2008.11.045

Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron* 33, 325–340. doi:10.1016/S0896-6273(02)00586-X

Clayton, N. S., and Dickinson, A. (1999). Scrub jays (Aphelocoma coerulescens) remember the relative time of caching as well as the location and content of their caches. *J. Comp. Psychol.* 113, 403–416. doi:10.1037/0735-7036.113.4.403

Colgin, L. L. (2011). Oscillations and hippocampal-prefrontal synchrony. *Curr. Opin. Neurobiol.* 21, 467–474. doi:10.1016/j.conb.2011.04.006

Colgin, L. L., Moser, E. I., and Moser, M. B. (2008). Understanding memory through hippocampal remapping. *Trends Neurosci.* 31, 469–477. doi:10.1016/j.tins.2008.06.008

Czerniawski, J., Yoon, T., and Otto, T. (2009). Dissociating space and trace in dorsal and ventral hippocampus. *Hippocampus* 19, 20–32. doi:10.1002/hipo.20469

DeVito, L. M., and Eichenbaum, H. (2010). Distinct contributions of the hippocampus and medial prefrontal cortex to the "what-where-when" components of episodic-like memory in mice. *Behav. Brain Res.* 215, 318–325. doi:10.1016/j.bbr.2009.09.014

Eichenbaum, H., Stewart, C., and Morris, R. G. (1990). Hippocampal representation in place learning. *J. Neurosci.* 10, 3531–3542.

Ergorul, C., and Eichenbaum, H. (2004). The hippocampus and memory for "what," "where," and "when". *Learn. Mem.* 11, 397–405. doi:10.1101/lm.73304

Ferbinteanu, J., and Shapiro, M. L. (2003). Prospective and retrospective memory coding in the hippocampus. *Neuron* 40, 1227–1239. doi:10.1016/S0896-6273(03)00752-9

Ferbinteanu, J., Shirvalkar, P., and Shapiro, M. L. (2011). Memory modulates journey-dependent coding in the rat hippocampus. *J. Neurosci.* 31, 9135–9146. doi:10.1523/JNEUROSCI.1241-11.2011

Ferino, F., Thierry, A. M., and Glowinski, J. (1987). Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex in the rat. *Exp. Brain Res.* 65, 421–426. doi:10.1007/BF00236315

Fortin, N. J., Agster, K. A., and Eichenbaum, H. (2002). Critical role of the hippocampus in memory for sequences of events. *Nat. Neurosci.* 5, 458–462.

Frank, L. M., Brown, E. N., and Wilson, M. (2000). Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27, 169–178. doi:10.1016/S0896-6273(00)00018-0

Gordon, J. A. (2011). Oscillations and hippocampal-prefrontal synchrony. *Curr. Opin. Neurobiol.* 21, 486–491. doi:10.1016/j.conb.2011.02.012

Griffin, A. L., Eichenbaum, H., and Hasselmo, M. E. (2007). Spatial representations of hippocampal CA1 neurons are modulated by behavioral context in a hippocampus-dependent memory task. *J. Neurosci.* 27, 2416–2423. doi:10.1523/JNEUROSCI.4083-06.2007

Griffin, A. L., Owens, C. B., Peters, G. J., Adelman, P. C., and Cline, K. M. (2012). Spatial representations in dorsal hippocampal neurons during a tactile-visual conditional discrimination task. *Hippocampus* 22, 299–308. doi:10.1002/hipo.20898

Hallock, H. L., and Griffin, A. L. (2013). Dynamic coding of dorsal hippocampal neurons between tasks that differ in structure and memory demand. *Hippocampus* 23, 169–186. doi:10.1002/hipo.22079

Hasselmo, M. E. (2009). A model of episodic memory: mental time travel along encoded trajectories using grid cells. *Neurobiol. Learn. Mem.* 92, 559–573. doi:10.1016/j.nlm.2009.07.005

Hasselmo, M. E., and Eichenbaum, H. (2005). Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Netw.* 18, 1172–1190. doi:10.1016/j.neunet.2005.08.007

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2005). Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus* 15, 739–749. doi:10.1002/hipo.20106

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2010). Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front. Integr. Neurosci.* 4:2. doi:10.3389/neuro.07.002.2010

Jay, T. M., Thierry, A. M., Wiklund, L., and Glowinski J. (1992). Excitatory Amino Acid Pathway from the Hippocampus to the Prefrontal Cortex. Contribution of AMPA Receptors in Hippocampo-prefrontal Cortex Transmission. *Eur. J. Neurosci.* 4, 1285–1295. doi:10.1111/j.1460-9568.1992.tb00154.x

Jay, T. M., and Witter, M. P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *J. Comp. Neurol.* 313, 574–586. doi:10.1002/cne.903130404

Ji, D., and Wilson, M. A. (2008). Firing rate dynamics in the hippocampus induced by trajectory learning. *J. Neurosci.* 28, 4679–4689. doi:10.1523/JNEUROSCI.4597-07.2008

Jones, M. W., and Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3:e402. doi:10.1371/journal.pbio.0030402

Lee, I., Griffin, A. L., Zilli, E. A., Eichenbaum, H., and Hasselmo, M. E. (2006). Gradual translocation of spatial correlates of neuronal firing in the hippocampus toward prospective reward locations. *Neuron* 51, 639–650. doi:10.1016/j.neuron.2006.06.033

Lenck-Santini, P. P., Save, E., and Poucet, B. (2001). Place-cell firing does not depend on the direction of turn in a Y-maze alternation task. *Eur. J. Neurosci.* 13, 1055–1058. doi:10.1046/j.0953-816x.2001.01481.x

Leutgeb, S., Leutgeb, J. K., Barnes, C. A., Moser, E. I., McNaughton, B. L., and Moser, M. B. (2005). Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* 309, 619–623. doi:10.1126/science.1114037

Lever, C., Wills, T., Cacucci, F., Burgess, N., and O'Keefe, J. (2002). Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature* 416, 90–94. doi:10.1038/416090a

Markus, E. J., Qin, Y. L., Leonard, B., Skaggs, W. E., McNaughton, B. L., and Barnes, C. A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J. Neurosci.* 15, 7079–7094.

McNaughton, B. L., Barnes, C. A., and O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp. Brain Res.* 52, 41–49. doi:10.1007/BF00237147

Moita, M. A. P., Rosis, S., Zhou, Y., LeDoux, J. E., and Blair, H. T. (2004). Putting fear in its place: remapping of hippocampal place cells during fear conditioning. *J. Neurosci.* 24, 7015–7023. doi:10.1523/JNEUROSCI.5492-03.2004

Muller, R. U., Bostock, E., Taube, J. S., and Kubie, J. L. (1994). On the directional firing properties of hippocampal place cells. *J. Neurosci.* 14, 7235–7251.

Muller, R. U., and Kubie, J. L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J. Neurosci.* 7, 1951–1968.

Muller, R. U., Stead, M., and Pach, J. (1996). The hippocampus as a cognitive graph. *J. Gen. Physiol.* 107, 663–694. doi:10.1085/jgp.107.6.663

Navratilova, Z., Hoang, L. T., Schwindel, C. A., Tatsuno, M., and McNaughton, B. L. (2012). Experience-dependent firing rate remapping generates directional selectivity in hippocampal place cells. *Front. Neural Circuits* 6:6. doi:10.3389/fncir.2012.00006

O'Keefe, J., and Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press.

Olton, D. S., Becker, J. T., and Handelmann, G. E. (1979). Hippocampus, space and memory. *Behav. Brain Sci.* 2, 313–365. doi:10.1017/S0140525X00062713

Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsaki, G. (2008). Internally generated cell assembly sequences in the rat hippocampus. *Science* 321, 1322–1327. doi:10.1126/science.1159775

Popa, D., Duvarci, S., Popescu, A. T., Léna, C., and Paré, D. (2010). Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proc. Natl. Acad. Sci. U.S.A.* 107, 6516–6519. doi:10.1073/pnas.0913016107

Rawlins, J. N., and Olton, D. S. (1982). The septo-hippocampal system and cognitive mapping. *Behav. Brain Res.* 5, 331–358. doi:10.1016/0166-4328(82)90039-0

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatr.* 20, 11–21. doi:10.1136/jnnp.20.1.11

Seidenbecher, T., Laxmi, T. R., Stork, O., and Pape, H. C. (2003). Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science* 301, 846–850. doi:10.1126/science.1085818

Siapas, A. G., Lubenov, E. V., and Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46, 141–151. doi:10.1016/j.neuron.2005.02.028

Siapas, A. G., and Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21, 1123–1128. doi:10.1016/S0896-6273(00)80629-7

Smith, D. M., and Mizumori, S. J. (2006). Learning-related development of context-specific neuronal responses to places and events: the hippocampal role in context processing. *J. Neurosci.* 26, 3154–3163. doi:10.1523/JNEUROSCI.3234-05.2006

Stanton, M. E., Thomas, G. J., and Brito, G. N. (1984). Posterodorsal septal lesions impair performance on both shift and stay working memory tasks. *Behav. Neurosci.* 98, 405–415. doi:10.1037/0735-7044.98.3.405

Stern, C. E., Sherman, S. J., Kirchhoff, B. A., and Hasselmo, M. E. (2001). Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. *Hippocampus* 11, 337–346. doi:10.1002/hipo.1048.abs

Tort, A. B., Kramer, M. A., Thorn, C., Gibson, D. J., Kubota, Y., Graybiel, A. M., et al. (2008). Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc. Natl. Acad. Sci. U.S.A.* 105, 20517–20522. doi:10.1073/pnas.0810524105

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204. doi:10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.3.CO;2-J

Wiener, S. I., Paul, C. A., and Eichenbaum, H. (1989). Spatial and behavioral correlates of hippocampal neuronal activity. *J. Neurosci.* 9, 2737–2763.

Wills, T. J., Lever, C., Cacucci, F., Burgess, N., and O'Keefe, J. (2005). Attractor dynamics in the hippocampal representation of the local environment. *Science* 308, 873–876. doi:10.1126/science.1108905

Wood, E. R., Dudchenko, P. A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. *Nature* 397, 613–616. doi:10.1038/17605

Wood, E. R., Dudchenko, P. A., Robitsek, R. J., and Eichenbaum, H. (2000). Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27, 623–633. doi:10.1016/S0896-6273(00)00071-4

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Differential cortical c-Fos and Zif-268 expression after object and spatial memory processing in a standard or episodic-like object recognition task

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Episodic memory reflects the capacity to recollect what, where, and when a specific event happened in an integrative manner. Animal studies have suggested that the medial temporal lobe and the medial pre-frontal cortex are important for episodic-like memory (ELM) formation. The goal of present study was to evaluate whether there are different patterns of expression of the immediate early genes c-Fos and Zif-268 in these cortical areas after rats are exposed to object recognition (OR) tasks with different cognitive demands. Male rats were randomly assigned to five groups: home cage control, empty open field (CTR-OF), open field with one object (CTR-OF + Obj), novel OR task, and ELM task and were killed 1 h after the last behavioral procedure. Rats were able to discriminate the objects in the OR task. In the ELM task, rats showed spatial (but not temporal) discrimination of the objects. We found an increase in the c-Fos expression in the dorsal dentate gyrus (DG) and in the perirhinal cortex (PRh) in the OR and ELM groups. The OR group also presented an increase of c-Fos expression in the medial prefrontal cortex (mPFC). Additionally, the OR and ELM groups had increased expression of Zif-268 in the mPFC. Moreover, Zif-268 was increased in the dorsal CA1 and PRh only in the ELM group. In conclusion, the pattern of activation was different in tasks with different cognitive demands. Accordingly, correlation tests suggest the engagement of different neural networks in the tasks used. Specifically, perirhinal-DG co-activation was detected after the what-where memory retrieval, but not after the novel OR task. Both regions correlated with the respective behavioral outcome. These findings can be helpful in the understanding of the neural networks underlying memory tasks with different cognitive demands.

Keywords: recognition memory, spatial memory, episodic memory, immediate early genes, plasticity, hippocampus

INTRODUCTION

Human episodic memory refers to our capacity to recall when and where a specific event (what) happened (Tulving, 2001, 2002; Dere et al., 2006). Some researchers have pointed out that it is a unique human capability, since only humans have autonoetic awareness (Tulving, 2002; Clayton et al., 2003; Dere et al., 2006). However, recently, researchers have found that other animals can also recollect what-where-when an episode occurred. Clayton et al. (2003) distinguished between the phenomenological criteria and the behavioral criteria and called this non-human memory system episodic-like memory (ELM). Some authors also described that animals can use these memories in an integrative manner, a fundamental issue in the episodic memory definition (Clayton et al., 2003; Dere et al., 2006; Kart-Teke et al., 2006). In this context, object recognition (OR) tasks have been used to accesses ELM in rodents.

The novel OR task accesses the capacity of rats in discriminating new objects from old ones in a familiar arena, being an important tool to investigate the "what" aspect of the ELM. Although hippocampal function is essential to human episodic memory (Squire and Zola, 1996; Tulving, 2002), the results regarding the role of this structure in the OR in rodents are controversial (Brown and Aggleton, 2001; Aggleton and Brown, 2006; Ainge et al., 2006). Conversely, lesions (Barker et al., 2007), temporary inactivation (Winters and Bussey, 2005b), or NMDA blockade in the perirhinal cortex (PRh) (Winters and Bussey, 2005a; Barker and Warburton, 2008) results in impairment of novel OR performance.

Variations of the OR task have been developed to study the spatial and temporal aspects of the ELM as well (Dere et al., 2007; Hoge and Kesner, 2007). Dere et al. (Dere et al., 2005a,b; Kart-Teke et al., 2006) developed an OR task in which mice or rats have to discriminate when and where they previously encountered a specific familiar object. Recently, we have adapted this protocol using a 24-h retention delay (Barbosa et al., 2010), in order to study separately the acquisition, consolidation, and retrieval mnemonic

processes. The use of this retention delay allows pharmacological manipulations, as well as the investigation of immediate early genes expression related to the ELM components.

Evaluation of immediate-early genes (IEGs) has been used to explore how different neural regions are recruited after a behavioral stimulation (Guzowski et al., 2004; Kubik et al., 2007). c-Fos protein is one of the most common markers of neuronal plasticity used in the field. Studies have described an increase in the expression of c-Fos in the PRh after rats were exposed to new visual stimuli, but not familiar ones (Wan et al., 1999, 2001). Interestingly, similar increases were not found in the hippocampus (HP) (Wan et al., 1999, 2001; Aggleton et al., 2012), which is in agreement with some lesion studies (Dix and Aggleton, 1999; Barker and Warburton, 2011). However, when rats were allowed to explore new or familiar objects (instead of single visual exposition to new or familiar stimuli) an increase in the c-Fos expression in the hippocampal subfields was reported (Albasser et al., 2010, 2013). Thus, actively exploring objects in a familiar arena engage hippocampal activity, although this region might not be essential in this task because lesions in this area do not elicit deficits (Mumby et al., 2002; Hoge and Kesner, 2007).

On the other hand, the engagement of the HP has been reported when spatial and/or temporal components are involved in the recognition task (Mumby et al., 2002; Hoge and Kesner, 2007; Barker and Warburton, 2011; Barbosa et al., 2012). In this respect, Castilla-Ortega et al. (2012) studied c-Fos activation after an ELM task in wild-type mice and LPA_1-null mice. In the task used in that study, the animals were supposed to discriminate between old and recent objects (temporal order) as well as the old-displaced and the old-stationary object (spatial memory). However, wild-type mice showed only what-when memory, which was impaired in the LPA_1-null mice. They found an increase in c-Fos expression in the dentate gyrus (DG), CA1 subregion, and in the medial prefrontal cortex (mPFC) in the normal mice. Unfortunately, this previous study included only a home cage control (CTR-HC) group, which limits the interpretation of the findings. Indeed, it has been demonstrated that environmental novelty *per se* can induce increase in c-Fos expression in the hippocampal formation (Jenkins et al., 2004; VanElzakker et al., 2008).

While c-Fos studies provide information regarding brain areas activation after a certain event, the IEG Zif-268 has been implicated in long-term memory consolidation (Bozon et al., 2002). Zif-268 knock-down mice are impaired in different spatial and non-spatial learning tasks, as well as in the expression of late LTP (Davis et al., 2000; Jones et al., 2001). Jones et al. (2001) showed that mutant mice lacking zif-268 gene were able to express early LTP in the DG, but not late LTP (after 24 or 48 h). Zif-268 has also been implicated in the novel OR and in object location tasks when there was a long interval between training and test (Bozon et al., 2003b). However, these studies did not evaluate the pattern of this IEG in different neural substrates. More recently, Soulé et al. (2008) found that object-in-place task induces an increase in *zif-268* in the rat DG. To our knowledge there are no studies addressing the pattern of Zif-268 expression in different cortices after variations of OR tasks (with different cognitive demands).

The goal of present study was to evaluate whether there are different patterns of expression of the immediate early genes c-Fos and Zif-268 in the medial temporal lobe structures and mPFC after animals are exposed to OR tasks with distinct cognitive demands. Although both IEGs are approached as plasticity markers, their co-activation in the same neural regions is not unequivocal (Herdegen and Leah, 1998; Bernabeu et al., 2006). We used the novel OR task and an ELM task. In the first task rats had to discriminate between new and familiar objects, while in the second animals had to discriminate familiar objects spatiotemporally. It is expected that different neural regions are engaged in this two recognition tasks. For example, while HP and mPFC are essential to spatiotemporal processing, they do not seem to be involved in the novel item recognition process (Hoge and Kesner, 2007; DeVito and Eichenbaum, 2010; Aggleton et al., 2012). In order to verify the specificity of the results of IEGs expression, we added not only CTR-HCs but also rats exposed to an empty open-field or to an open-field with one novel object.

MATERIALS AND METHODS

ANIMALS

Thirty-nine 3-month old male Wistar rats (250–400 g) were housed under controlled temperature (25 ± 1°C) and a 12/12 h light/dark cycle (lights on at 6.30 a.m.). Food and water were offered *ad libitum*. All animals were handled for 10 min/day for 5 days before the experiments start. The rats were handled accordingly to Brazilian law for the use of animals in scientific research (Law Number 11.794) and all procedures were approved by the local ethics committee (protocol number 049/2012). All efforts were made to minimize animal pain, suffering, or discomfort as well as the number of rats used.

APPARATUS AND OBJECTS

The behavioral tests were conducted in a circular open-field (84 cm in diameter surrounded by a 32-cm height wall), made of wood and painted in black. There were external visual cues in the room that rats could use for spatial learning. Three sets of objects (made of plastic and filled with cement to ensure that animals would not displace them) were used in a random manner among the experiments. The objects used included a sugar bowl, a mug, and a goblet. They differed in height (9–12 cm), width (6–10 cm), color, and shape. The apparatus and objects were cleaned with a 5% alcohol/water solution after each behavioral session. A previous experiment with other rats demonstrated no spontaneous preference for any of these objects. The sessions were recorded by a digital camera placed above the apparatus. The behavioral parameters were registered by an animal tracking software (Anymaze, Stoelting, USA).

EXPERIMENTAL DESIGN

Experimental design is schematized in **Figure 1**. The animals were divided into five groups: CTR-HC ($n = 8$), open-field control ($n = 8$), open-field + object control ($n = 6$), OR task ($n = 8$), and ELM task ($n = 9$). Twenty-four hours prior to the beginning of the tasks, all animals underwent a 10-min habituation session in the open field, except for the CTR-HC group. Each session was performed in an interval of 24 h, except for the two training sessions

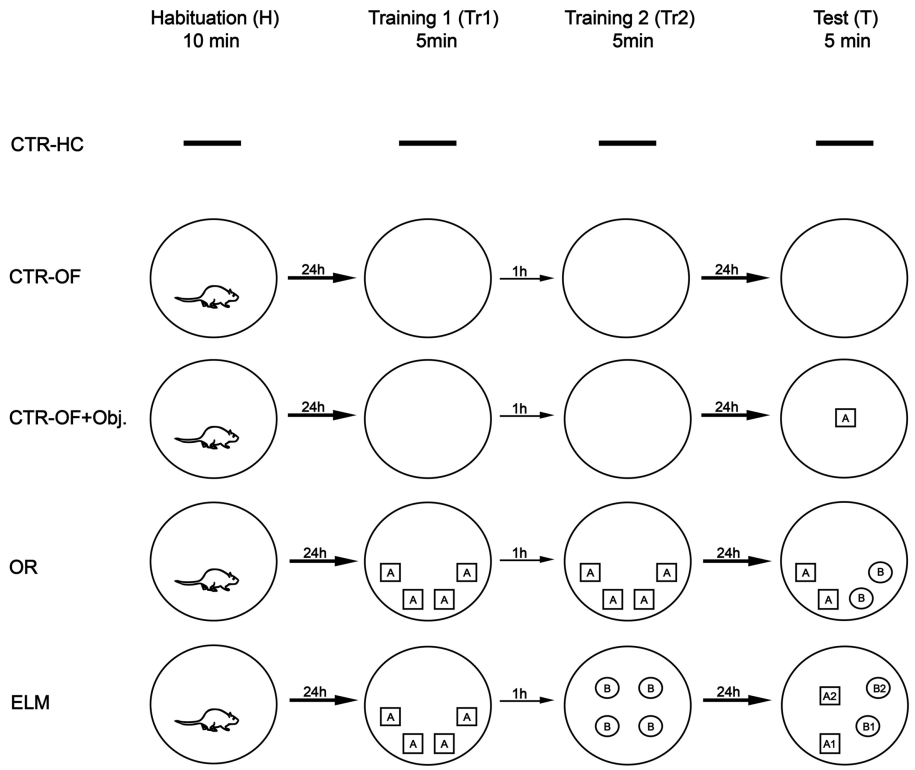


FIGURE 1 | Experimental procedure. CTR-HC, home cage control (without behavioral sessions); CTR-OF, open field control (four expositions to the empty open field); CTR-OF + Obj, open field + object control (exposition to an object in the last behavioral session); OR, object recognition task (discrimination between novel and familiar objects); ELM, episodic-like memory task (spatiotemporal discrimination of familiar objects).

that were performed with an interval of 1 h between them. The behavioral procedures for each group were the following:

(1) CTR-HC: on the sixth day after the handling, the animals were removed from their home cages and euthanized without apparatus exposure. The goal of this group was to measure IEGs basal expression;
(2) Open-field control (CTR-OF): the animals were euthanized after four expositions to the open-field without any objects. The goal of this group was to control IEGs expression as consequence of exploring a familiar arena;
(3) Open-field + object control (CRT-OF + Obj): the rats were exposed to the empty apparatus during the habituation and two training sessions, and to a test session in the open-field with one object placed in a random location. The goal of this group was to control IEGs expression as result from sensory activity. Only one object was placed in order to avoid mnemonic processes (comparing objects in different locations);
(4) OR: the animals were submitted to the habituation session, two training sessions with four copies of one object in the same positions on both trials and a test session with two copies of objects used in the training sessions and two novel objects (in the same locations). The exploration rates in the test session were expected to be higher for novel objects than for familiar objects;
(5) ELM task: this task consisted of a habituation session, two training trials and a test session. In the first training, the animals were placed in the open-field with four copies of an object in a certain spatial configuration. After 1 h, in the second training, they were submitted to a set of four copies of another object in a different spatial configuration. Spatial configurations were random across subjects. In the test session, two copies of the objects from each training session were presented. One copy from the first trial was placed in the same location (old familiar-stationary) and the other copy was placed in a new location (old familiar-displaced). The same procedure was conducted with the recent familiar objects (those presented in the second training). According to Kart-Teke et al. (2006, 2007), the animals were expected to explore the recent displaced object more than the recent stationary object, and the opposite pattern is expected regarding the old objects. This inverse pattern would indicate that the rats integrated the "what-where-when" components of the ELM, contrary to similar ELM tasks (Dere et al., 2005a; Barbosa et al., 2010).

IMMUNOHISTOCHEMISTRY

Sixty minutes after the last behavioral procedure, rats were deeply anesthetized with intraperitoneal injection of the sodium thiopental (40 mg/kg) and perfused transcardially with 200 ml of phosphate-buffered saline (PBS), pH 7.4, containing 500 IU

heparin (Liquemin, Roche, Brazil), followed by 300 ml of 4.0% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4 (fixative solution). This interval was required aiming the expression peaks of Zif-268 and c-Fos (Bisler et al., 2002). The brains were removed from the skull, post-fixed in fixative solution for 2–4 h, and transferred to a solution containing sucrose 30% in 0.1 M PBS, pH 7.4. Each brain was serially cut in the coronal plane into 30-μm thick sections with a cryostat microtome (Leica, Germany) at a temperature of −20°C. The sections were placed sequentially in five compartments (one section per compartment), with the distance between one section and the next in the same compartment being approximately 150 μm. All sections were stored in antifreeze solution. For the detection of c-Fos and Zif-268, free-floating sections were incubated for 18–24 h with a monoclonal primary antibody raised in rabbits (Zif-268 antibody, SantaCruz Biotechnology, and c-Fos antibody, Oncogene Science, Cambridge, UK; both diluted 1:1000), containing 2% goat normal serum (Sigma Chemical Company), diluted in 0.3% Triton X-100 (ICN Biomedicals), and 0.1 M phosphate buffer, pH 7.4. Afterward, the sections were incubated with the biotinylated secondary anti-rabbit antibody raised in goat (1:1000; Jackson), also diluted in 0.3% Triton X-100 and 0.1 M phosphate buffer, pH 7.4. This procedure lasted 2 h and was performed at room temperature. Shortly after, the sections were washed and incubated in 2% avidin-biotin-peroxidase solution (ABC Elite kit, Vector Labs, Burlingame, CA, USA) for 90 min. The reaction was developed by the addition of 2.5% diaminobenzidine tetrahydrochloride (Sigma, St. Louis, MO, USA) and 0.01% H_2O_2 in 0.1 M phosphate buffer, pH 7.4. The sections were washed (four times, 5 min) with 0.1 M phosphate buffer, pH 7.4, between each step and at the end of the procedure. Afterward, the sections were dried, dehydrated in a graded alcohol series, cleared in xylene, and coverslipped with Entellan (Merck).

IMAGE ANALYSES AND CELL COUNT

Sections were examined under brightfield illumination (Olympus Microscope, BX-41). Images were captured using a CCD camera (Nikon, DXM-1200) and the locations of areas were determined using the atlas of Paxinos and Watson (2007). The cell count was performed manually in three sections per animal, through Image J software (1.46i, NIH) and the mean count was calculated and used in the analysis. Positive c-Fos and Zif-268 cells were counted in areas of the PRh, entorhinal cortex (ERH), dorsal hippocampal subregions (CA1, CA3, and DG), HP (calculated by the sum of the values of the three subregions), mPFC, and primary visual cortex (V1). The experimenter was blinded to experimental groups during counting. The number of cells for each brain area was normalized by mean values of the control group (CTR-HC).

DATA COLLECTION AND ANALYSIS

The parameters analyzed in the open-field were total distance traveled and time and exploration ratio of objects. The analyses were made by an experimenter blind to groups, who used keys to score exploration when the animals approached an object and had physical contact with it, either with the forepaws and/or snouts. The exploration ratio was the time exploring an object/total time exploring all objects. Object exploration ratios were calculated for novel objects in the OR task and displaced, stationary, old familiar, and recent familiar objects in the ELM task. The Kolmogorov–Smirnov test indicated normal data distribution. One-way ANOVAs were performed for total distance traveled and total time exploring the objects in the last session to analyze possible difference in motivation between groups. *A priori* planned dependent *t*-tests were used to compare novel and familiar objects in the OR group, considering the initial 2 min of the test session as suggested by others as the optimal time window analyses (Dix and Aggleton, 1999; Mumby et al., 2002). In the ELM task, displaced old familiar × stationary old familiar, and displaced recent familiar × stationary recent familiar were compared by dependent *t*-tests considering the total time of the test session (5 min). One-way ANOVAs were used for comparison of the number of positive Zif-268 or c-Fos neurons between groups in each brain area. *Post hoc* analysis was conducted with the Tukey–Kramer's test. Pearson's test was used to investigate correlations (r) for the cell count values among areas, as well as between behavioral parameters and cell count values in each area. Only areas that showed significant increase in the IEGs expression were included in the correlation analysis. Results were expressed as mean ± SEM. In all statistical tests, effects were considered significant when $p < 0.05$.

RESULTS

BEHAVIORAL TASKS

One-way ANOVA showed no significant differences in the total distance traveled in the habituation [$F(3,27) = 0.84$, $p = 0.483$], training 1 [$F(3,27) = 1.64$, $p = 0.203$], and training 2 [$F(3,27) = 0.79$, $p = 0.509$] sessions. Significant differences were detected in the total distance traveled in the test session [$F(3,27) = 3.39$, $p = 0.032$]. The Tukey–Kramer's *post hoc* revealed increased distance traveled by ELM group when compared to the CTR-OF group in the test session ($p = 0.028$; see **Table 1**). However, in this session, no differences were found in the total time of object exploration [$F(2,20) = 0.76$, $p = 0.481$], suggesting that all groups exposed to objects (CTR-OF + Obj, OR and ELM) present similar motivation to explore (see **Table 1**).

As expected, the rats submitted to the OR task presented an increase in the exploration ratio of novel objects when compared to exploration of the old object in the test session [$t(7) = 2.45$; $p = 0.044$, two-tailed *t*-test for paired samples], as shown in **Figure 2**. During the training sessions 1 and 2, there were no differences in the exploration ratio of the objects [$F(3,21) = 1.63$, $p = 0.212$ and $F(3,21) = 1.59$, $p = 0.220$, respectively, data not shown].

During the training sessions 1 and 2 of the ELM task there were no differences in the exploration ratio of similar objects [$F(3,21) = 2.57$, $p = 0.132$ and $F(3,21) = 1.16$, $p = 0.339$, respectively]. In the test session, the rats presented increased exploration ratio of the displaced old familiar object compared to the stationary old familiar object [$t(8) = 2.86$; $p = 0.021$]. No difference was found when the exploration ratios of the recent familiar objects were compared [$t(8) = 0.98$; $p = 0.354$], as shown in **Figure 3**.

c-Fos EXPRESSION

For the number of c-Fos-positive cells, one way ANOVA revealed significant differences between groups for HP [$F(4,34) = 5.96$, $p = 0.001$], DG [$F(4,34) = 16.51$, $p < 0.001$],

Table 1 | Total distance traveled (m) and total object exploration time (s) by groups in each session (mean ± SEM).

	CTR-OF	CTR-OF + Obj	OR	ELM
TOTAL DISTANCE (m)				
Habituation	27.82 ± 2.30	30.44 ± 3.49	29.43 ± 2.85	33.32 ± 2.22
Training session-1	14.44 ± 1.70	16.28 ± 3.18	16.08 ± 2.60	20.96 ± 1.92
Training session-2	9.44 ± 2.27	11.91 ± 2.22	12.71 ± 0.98	13.35 ± 2.15
Test	6.86 ± 1.62	13.08 ± 1.65	10.63 ± 2.16	13.93 ± 1.43*
TOTAL EXPLORATION (s)				
Training session-1	–	–	52.08 ± 12.18	64.69 ± 9.86
Training session-2	–	–	42.55 ± 10.34	45.03 ± 7.74
Test	–	33.32 ± 7.16	48.35 ± 12.45	48.88 ± 6.98

*CTR-OF, open-field control; CRT-OF + Obj, open-field + object control; OR, object recognition task; and ELM, episodic-like memory task. *$p < 0.05$ compared to CTR-OF (one-way ANOVA and Tukey–Kramer's post hoc).*

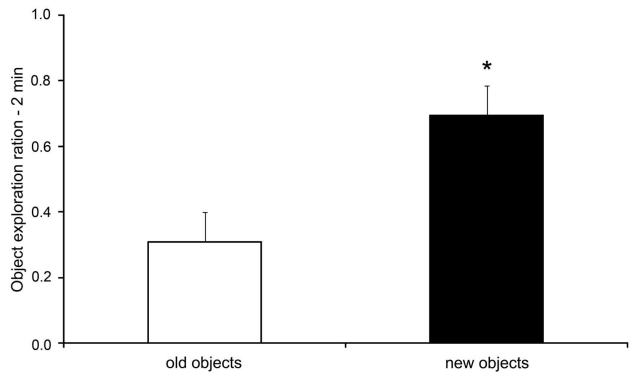


FIGURE 2 | Exploration ratios (mean + SEM) within the initial 2 min of the test session of the object recognition task. *$p < 0.05$ compared to old objects exploration (paired samples *t*-test).

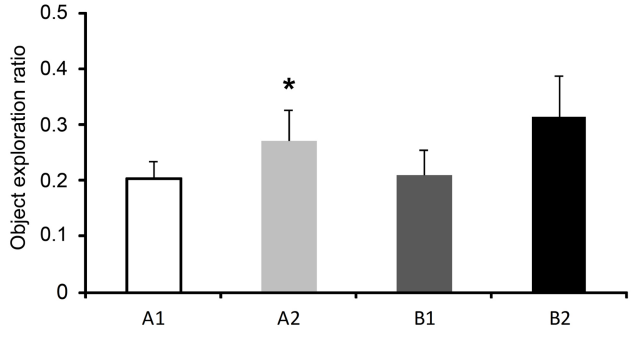


FIGURE 3 | Exploration ratios (mean ± SEM) within 5 min of the test session of the episodic-like memory (ELM) task. Objects: A1, stationary old familiar; A2, displaced old familiar; B1, stationary recent familiar; and B2, displaced recent familiar. *$p < 0.05$ compared to A1 (paired two-tailed *t*-test).

mPFC [$F(4,34) = 3.88$, $p = 0.011$], ERH [$F(4,34) = 3.37$, $p = 0.020$], and PRh [$F(4,34) = 8.32$, $p < 0.001$]. No differences were detected in the CA1 [$F(4,34) = 1.48$, $p = 0.228$], CA3 [$F(4,34) = 1.45$, $p = 0.238$], and V1 [$F(4,34) = 1.69$, $p = 0.174$]. *Post hoc* analysis revealed increased number of c-Fos-positive cells in the OR group compared to CTR-HC and CTR-OF in HP, DG, mPFC, and PRh. The number of c-Fos-positive-cells was also increased in ELM when compared to CTR-HC, CTR-OF, and CTR-OF + Obj in HP, DG, and PRh. ELM also showed increased number of c-Fos positive cells when compared to OR in DG. Mean results for counts in all groups are shown in **Figure 4**, and representative images of some areas are displayed in **Figure 5**.

Zif-268 EXPRESSION

For the number of Zif-268-positive cells, one way ANOVA revealed significant differences between groups in HP [$F(4,34) = 3.62$, $p = 0.005$], DG [$F(4,34) = 2.94$, $p = 0.034$], CA1 [$F(4,34) = 6.57$, $p < 0.001$], mPFC [$F(4,34) = 21.19$, $p < 0.001$], and PRh [$F(4,34) = 8.39$, $p < 0.001$]. No differences were detected in the CA3 [$F(4,34) = 0.59$, $p = 0.669$], V1 [$F(4,34) = 1.08$, $p = 0.380$], and ERH [$F(4,34) = 2.22$, $p = 0.087$]. *Post hoc* analysis revealed increased number of Zif-268-positive cells in OR group when compared to CTR-HC, CTR-OF, and CTR-OF + Obj in the mPFC. The analysis also showed increased number of Zif-268-positive cells in mPFC and PRH of the ELM group when compared to the three other groups. In addition, increased values were found in HP of this group compared to CTR-HC and CTR-OF. ELM also showed increased values when compared to CTR-OF + Obj in mPFC and PRh, as well as compared to OR in PRh and CA1. Although one-way ANOVA revealed significant differences between groups in the DG, differences were not detected by the Tukey–Kramer's *post hoc* test. Mean results for counts in all groups are shown in **Figure 6**, and representative images of some areas are displayed in **Figure 7**.

CORRELATIONS

Pearson's correlation tests were applied to the number of c-Fos and Zif-268 positive neurons in each area against the exploration rate of objects for each task. We also ran correlations of the number of c-Fos and Zif-268 positive neurons among areas that showed increase in the IEGs expression in the previous analyses (CA1, DG, PRh, and mPFC) after OR and ELM tasks. These correlations are shown in **Table 2**. Values (r; p) for non-significant correlations

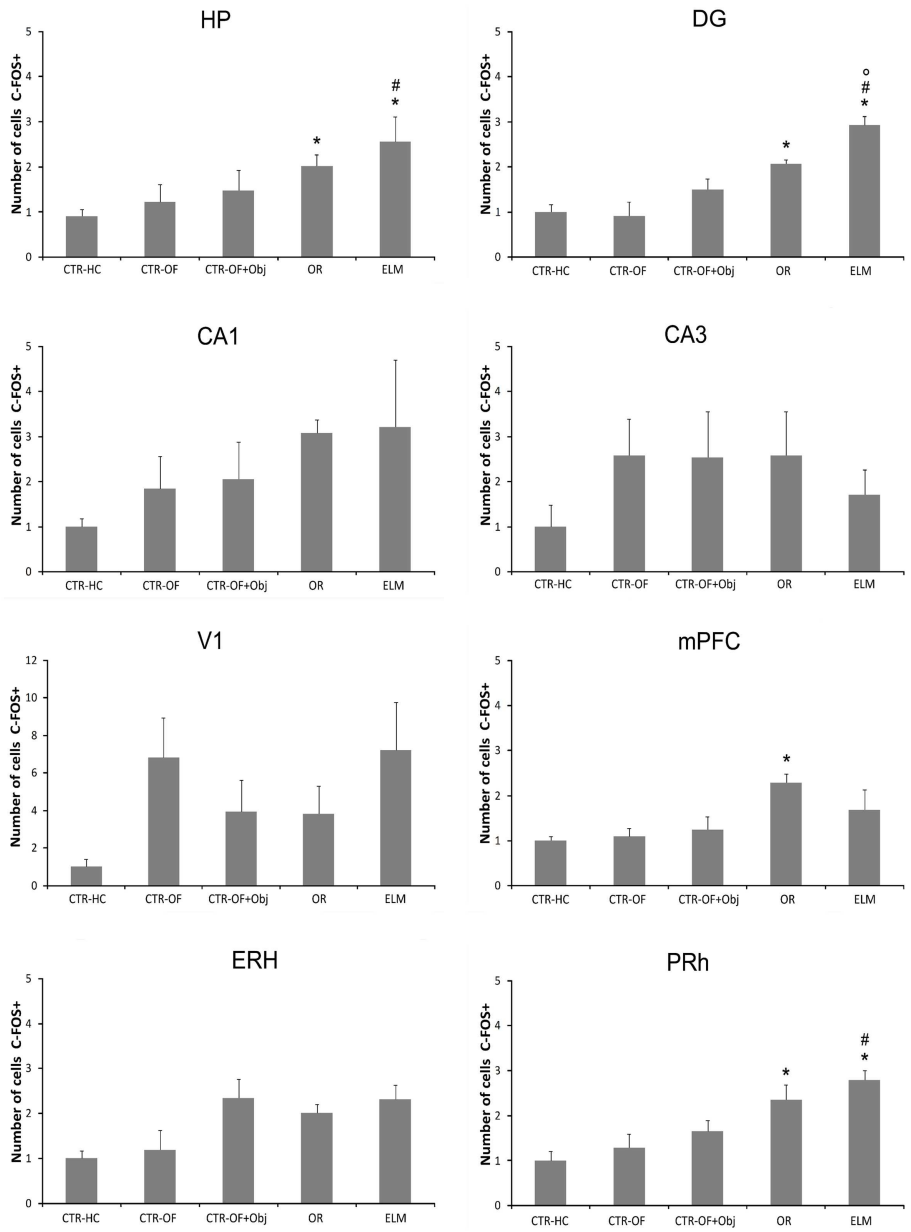


FIGURE 4 | Expression of c-Fos in different brain areas (HP, hippocampus; DG, dentate gyrus; CA1; CA3; mPFC, medial prefrontal cortex; V1, visual area 1; ERH, entorhinal cortex; PRh, perirhinal cortex) for home cage control (CTR-HC), open-field control (CTR-OF), open-field + object control (CRT-OF + Obj), object recognition (OR), and episodic-like memory (ELM) groups. The normalized number of cells is expressed as the mean ± SEM. $^{*}p < 0.05$ compared to CTR-HC and CTR-OF; $^{\#}p < 0.05$ compared to CTR-OF + Obj; $^{\circ}p < 0.05$ compared to OR (one-way ANOVA followed by Tukey's test).

were omitted. As shown in the table, all coefficients (r) were above 0.6, indicating large effect sizes for the correlations found.

DISCUSSION

We evaluated whether OR tasks with different cognitive demands produce a varied pattern of expression of the IEGs c-Fos and Zif-268 in the medial temporal lobe structures and in the mPFC. We found a greater c-Fos and Zif-268 expression in the dorsal HP, perirhinal, and mPFC in the ELM and OR groups when compared to the different control groups. This indicates that the activation of these structures is neither a consequence of exploration of a familiar arena nor due to the process of object exploration. More importantly, we found some differences between the activation of neural networks induced by the ELM and OR protocols. Specifically, the first one promoted increased c-Fos expression in the DG and increased Zif-268 expression in the PRh and CA1 compared to the OR, indicating a greater involvement of these regions in the retrieval of the task with spatial cognitive demand (as discussed

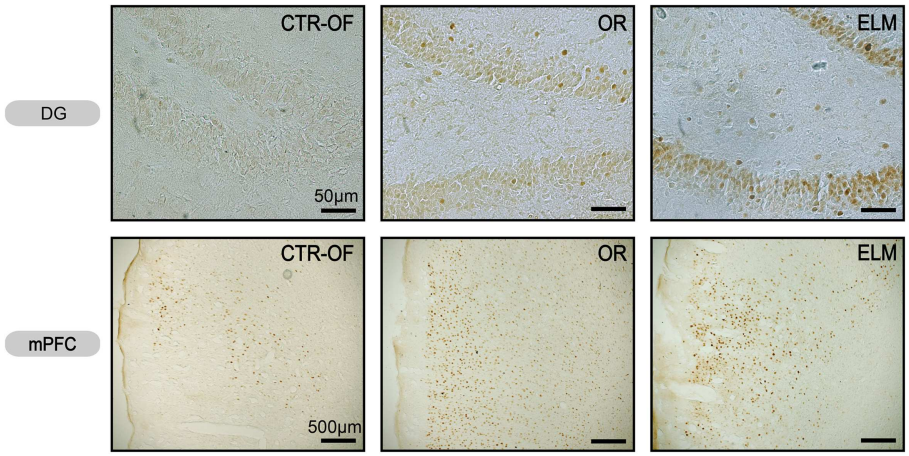


FIGURE 5 | Representative images of c-Fos expression in dentate gyrus (DG) and medial prefrontal cortex (mPFC) from subjects of control open-field + object (CTRL-OF + Obj), novel object recognition (OR), and episodic-like memory (ELM) task groups.

in detail below). As commented in the Section "Introduction," increases in IEGs expression in the hippocampal regions and in the prefrontal cortex after the ELM task were expected. However, unexpectedly, an increase in the Zif-268 expression in the PRh was also found.

As expected to the OR task, rats explored more the new objects when compared to the old objects, indicating recognition memory (see **Figure 2**). It has been suggested that the recognition memory is supported by two distinctive cognitive processes: familiarity and recollection (Brown and Aggleton, 2001; Eichenbaum et al., 2007). In the OR task, rats could use only familiarity to discriminate the objects. On the other hand, in the ELM task rats had to use the recollection process to discriminate the order of presentation and positions of the objects (Dere et al., 2006; Kart-Teke et al., 2006). In this task, we expected that rats would spend more time exploring the displaced recent object when compared to the stationary recent object, and the opposite pattern is expected to the old familiar objects (Kart-Teke et al., 2006, 2007; Li and Chao, 2008). Kart-Teke et al. (2006) suggested that this inverse pattern would be indicative that Wistar rats created an integrative what-where-when memory. However, in the present study, we did not found the same pattern of results. Rats spent more time exploring the displaced when compared to the stationary old familiar object and did not discriminate the recent familiar objects. Therefore, we cannot assume that the rats recalled a what-where-when memory. It is important to note, however, that in the present study we used a 24-h interval and not a 1-h delay as used by Kart-Teke and colleagues. This variation in the protocol could explain these different results. We have decided to use this interval to avoid a possible ceiling effect in the IEGs expression, as well to separate the retrieval mnemonic process from the acquisition and consolidation processes (Bisler et al., 2002; Barbosa et al., 2010). Regardless, the present results clearly show that rats used associative recognition memory, because they could discriminate spatially the old familiar objects, similarly to the object-in-place task used by others (Dix and Aggleton, 1999; Barker et al., 2007). In addition, it has been demonstrated that the OR and object-in-place tasks are supported by different neural substrates (Mumby et al., 2002; Barker et al., 2007; Barker and Warburton, 2011), and this finding was also reported here regarding OR and ELM tasks, as discussed below. Thus, in the present study, we can assume that rats accessed at least what-where aspects of the ELM. For this reason we discuss the outcome of the ELM task in terms of what-where memory or spatial memory.

Regarding c-Fos expression (**Figures 4** and **5**), we found a greater activation of the DG in the ELM task when compared to all other groups; including the novel OR task. The DG has been implicated in the detection of spatial novelty (Kesner, 2007; Leutgeb et al., 2007; Hunsaker and Kesner, 2008; Hunsaker et al., 2008), and some theoretical authors have suggested that this structure is essential to the spatial pattern separation (McClelland et al., 1995; Norman and O'Reilly, 2003; Treves et al., 2008). Accordingly, we have shown that temporary inactivation of this region can impair the what-where acquisition and/or consolidation processes (Barbosa et al., 2012). Muscimol injection before the first training session produced impairment in the spatial novelty detection, but not in the temporal order memory. Therefore, the increase in c-Fos expression seems in agreement with previous studies. However, it is important to note that we accessed IEG expression after the test session and therefore, in the present work, we analyzed a different mnemonic process. More studies are necessary to verify a causal relation between this HP region and retrieval of spatial memory.

Contrary to previous studies (Albasser et al., 2010, 2013; Rinaldi et al., 2010; Castilla-Ortega et al., 2012), we did not found any difference in the c-Fos expression in the dorsal CA1 and CA3 subregions. Castilla-Ortega et al. (2012) described an increase in c-Fos expression in the CA1 subregion after ELM task, but no alterations in CA3 compared to the home cage group. It is important to point out that this previous study had a 90-min delay before retrieval while in the present study we used a 24-h delay between the second sample and the test session. More importantly, the mice in that previous study did not discriminate the displaced familiar object (that

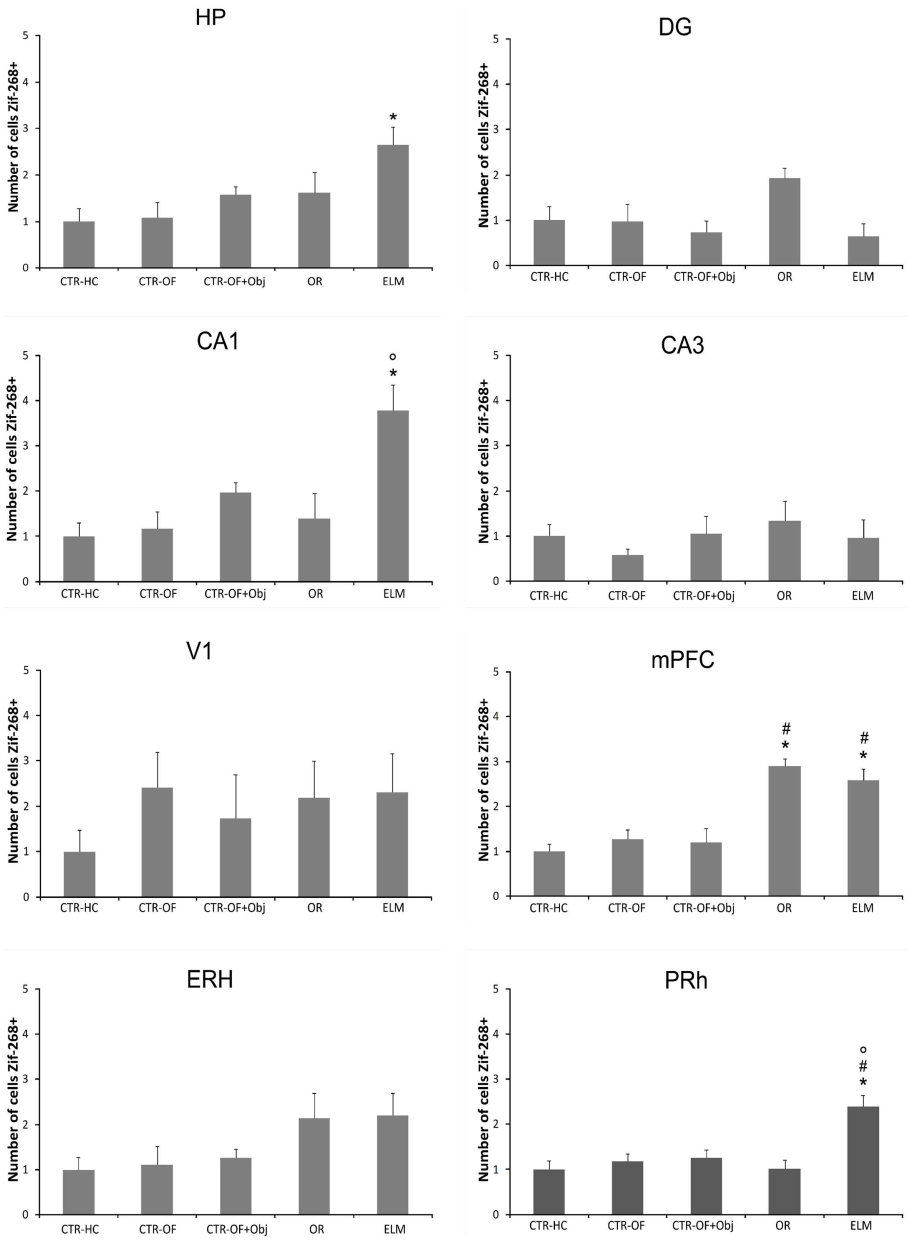


FIGURE 6 | Expression of Zif-268 in different brain areas (HP, hippocampus; DG, dentate gyrus; CA1; CA3; mPFC, medial prefrontal cortex; V1, visual area 1; ERH, entorhinal cortex; PRh, perirhinal cortex) for home cage control (CTR-HC), open-field control (CTR-OF), open-field + object control (CRT-OF + Obj), object recognition (OR) episodic-like memory (ELM) task groups. The normalized number of cells is expressed as the mean ± SEM. $^{*}p < 0.05$ compared to CTR-HC and CTR-OF; $^{\#}p < 0.05$ compared to CTR-OF + Obj; $^{\circ}p < 0.05$ compared to OR (one-way ANOVA followed by Tukey's test).

was the only displaced object in that study). Further, we also added other control groups beyond the home cage, as a way to control other possible variables that could interfere with IEGs expression as exploratory activity in the open-field and object exploration *per se*. Albasser and collaborators (Albasser et al., 2010; Aggleton et al., 2012) found a greater c-Fos expression in the dorsal CA3 subregion in rats exposed to novel objects when compared to rats exposed to familiar objects. The behavioral protocol in this case is very dissimilar from the present one, since rats were exposed in multiple trials to novel or familiar objects in a bow-tie-shaped maze. However, hippocampal lesion did not impair novelty object discrimination in that task (Albasser et al., 2013).

No difference was detected in the c-Fos expression in the lateral entorhinal between the groups. This medial temporal lobe region has been implicated in item novelty detection. Indeed, Hunsaker et al. (2013) showed that excitotoxic lesion of the lateral ERH (but

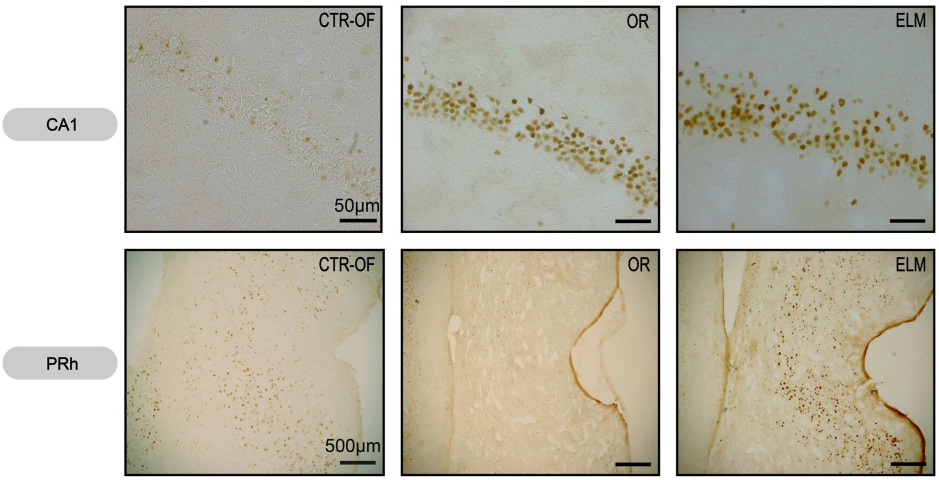


FIGURE 7 | Representative images of Zif-268 expression in CA1 hippocampal subregion and perirhinal cortex (PRh) from subjects of control open-field + object (CTRL-OF + Obj), novel object recognition (OR), and episodic-like memory (ELM) task groups.

Table 2 | Correlations to the number of c-Fos and Zif-268 positive neurons in the analyzed areas against the exploration rate of objects during novel object recognition (OR) or episodic-like memory (ELM) task.

	OR	ELM
	Familiar objects exploration ratio (2 min)	**Displaced familiar object exploration ratio (5 min)**
c-Fos		PRh (0.71; 0.032)
Zif-268	PRh (0.79; 0.020)	DG (0.66; 0.050)* PRh (0.79; 0.010) DG-PRh (0.71; 0.02)[a]

*Areas: hippocampal area (dentate gyrus – DG), and perirhinal cortex (PRh). Significant correlations (Pearson's correlation – r) when $p < 0.05$. *Marginally significant effects.*

[a] *Significant correlations shown by Pearson's test (r; p) to the number of Zif-268 positive neurons between areas after episodic-like memory (ELM) task.*

not the medial portion) disrupted novel OR memory. Interestingly, the medial entorhinal lesion impaired contextual novelty detection, but not the detection of a novel item. However, we did not found any change in the IEGs expression analyzed here in this area. It is important to point out that we found a tendency ($p = 0.08$) toward an increase in Zif-268 expression in this region. Thus, with a larger sample size we would probably find a significant difference. More studies are needed to evaluate better the role of the lateral ERH in the retrieval of recognition memory.

Regarding perirhinal c-Fos expression, no difference was detected between OR and ELM groups, but both had increased number of positive cells relative to the control groups. These two groups were exposed to four objects in the test session, which was not the case of the home cage and open field groups (not exposed to any objects) and the open field plus one object group (explored only one object). Several studies have proposed that this region is fundamental to item novelty detection (Winters and Bussey, 2005a,b; Barker and Warburton, 2008), and more recently, lesion studies indicated also a role in the object-in-place task (Barker et al., 2007; Barker and Warburton, 2011). Therefore, this region seems to be essential in both OR tasks and the present results corroborate this idea.

Although lesion studies indicate that the mPFC is not involved in the detection of a novel item (Barker et al., 2007; Barker and Warburton, 2011; DeVito and Eichenbaum, 2011), some authors found an increase in the c-Fos expression after rodents were exposed to an OR memory task (Rinaldi et al., 2010; Castilla-Ortega et al., 2012). We also found increased activation of this area in the OR group when compared to the control groups. However, no difference was found between the OR and ELM groups, corroborating the previous finding by Castilla-Ortega et al. (2012). On the other hand, studies with lesions have showed a role of this region in the object-in-place task, as well as an interaction of the mPFC with the HP (Barker and Warburton, 2011). Kim et al. (2011) showed that in object-in-place learning "CA1-mPFC coherence in theta oscillation was maximal before entering a critical place for decision making," which indicates an integrative role of these neural regions. Interestingly, we found a greater expression of Zif-268 in the OR and ELM relative to all the control groups. As one can see, only in these two tasks rats had to make some decision. Thus it seems quite possible that the mPFC is involved in this cognitive process, although lesion studies indicate that, at least in the item recognition, it is not always determinant to the output behavior. Another possible explanation to the involvement of this region is related to the previously reported role of mPFC in the long term memory consolidation and recall processes (Frankland and Bontempi, 2005; Leon et al., 2010).

Immediate-early genes expression data indicated that there were different neural networks involved considering the activation pattern of OR and ELM groups. Thus, we investigated possible co-activations between structures as evaluated by IEGs expression, as well as correlation between activation of structures and output

behavior (**Table 2**) in groups that went through OR and ELM tasks. In the ELM task, a positive correlation between the PRh c-Fos expression and the displaced old familiar object exploration ratio was found. This result is in agreement with lesion studies indicating a role of this structure in the object-in-place task (Barker et al., 2007; Barker and Warburton, 2011). It is important to note, however, that these are correlation findings which do not imply causal relations between IEGs expressions and the behavioral outcomes.

There are few studies evaluating the involvement of Zif-268 expression in recognition memory. It is known that the *zif-268* gene expression is involved in the consolidation of item and memory location of objects (Bozon et al., 2003a,b). Soulé et al. (2008) showed that the *zif-268* expression was elevated in the DG after rats were exposed to an object location task. As mentioned above, we found an increase in c-Fos expression in the DG only after what-where memory retrieval. This group also had the greatest Zif-268 expression in the dorsal CA1 subregion (**Figures 6** and **7**). In this respect, we have recently shown that temporary inactivation of CA1 subregion before training impairs both temporal and spatial components of the ELM, which is in accordance with the present results (Barbosa et al., 2012).

The ELM rats had also the greatest Zif-268 expression in the PRh (**Figures 6** and **7**). As commented before, this region has been pointed as critical to object-in-place task (Brown and Aggleton, 2001; Aggleton et al., 2012). Again our results are in agreement with these lesion studies. Additionally, a positive correlation between the perirhinal Zif-268 expression and the familiar objects exploration ratio was detected (**Table 2**). Interestingly, to our knowledge, this is the first study to show a positive correlation between Zif-268 expression and time that rats spent exploring familiar objects. Previous studies showed a negative correlation between perirhinal c-Fos activity and exploration of familiar stimuli (Wan et al., 1999, 2001), which was not detected in the present work.

We also found different neural networks co-activated in the ELM group (**Table 2**), regarding Zif-268 expression. Interestingly, PRh activity was correlated with DG. The co-activation of the PRh with DG corroborates studies indicating that both the HP and this medial temporal lobe region are recruited in the object-in-place task (Barker and Warburton, 2011). Moreover, our results suggest that CA1 does not co-activate with the PRh during this task. In this context, it is known that the PRh cortex has direct projections to the CA1 subfield, and indirect connections, via lateral ERH, to DG and CA3 (van Strien et al., 2009; Kealy and Commins, 2011). Probably the most important finding here was the positive correlation between both DG and PRh Zif-268 expressions and the displaced familiar object exploration ratio. Interestingly, these results seem to corroborate the Binding of Items and Context (BIC) model that proposes that item memory (what) is processed preferentially in the PRh cortex (and the lateral ERH) and that the contextual information is processed initially in the medial ERH, while item and contextual elements would be bound together in the HP (Eichenbaum et al., 2007; Hunsaker et al., 2013). Indeed, as mentioned, we found co-activation of the PRh and DG in the ELM task used here. In addition, both neural areas positively correlated with the behavioral output, although the significance was marginal in the case of the DG.

It is important to note that the differential IEGs expression across the groups did not follow the same pattern when c-Fos and Zif-268 are considered. In this respect, although these IEGs are both involved in plastic processes, they have different biochemical routes (Bisler et al., 2002; Davis et al., 2003) and probably different functions. Additionally, while c-Fos has mostly been implicated in the exposure to novel stimuli, or as a consequence of stimulation after sensory deprivation, Zif-268 expression is probably related to persistent synaptic stimulation (see Chaudhuri et al., 2000). Indeed, it has been shown that Zif-268 is required for different types of learning, including OR-based tasks (Jones et al., 2001; Bozon et al., 2002). The implication for the present results is that the increased c-Fos expression after both OR and ELM tasks (that were, in general, similar across areas) would be related to the novelty present in the test situation compared to previous sessions. Conversely, the increased Zif-268 expression could reflect the activation of the structures engaged in plastic mechanisms related to the retrieval of the tasks. Accordingly, areas suggested to be more implicated in consolidation of spatial and temporal aspects of an event rather than standard OR tasks were activated after ELM, but not OR task.

Finally, it is important to point out that the differences found in IEGs expression cannot be explained by a general activation, because we did not detected any differences in the expression of c-Fos and Zif-268 in the control area V1. In addition, the groups did not presented differences in the total amount of object exploration in the last behavioral session. Thus, it is unlikely that the pattern of IEGs expression described here is a consequence of motor and/or sensory activity.

In conclusion, the present data show increased IEGs expression in brain areas related to memory processes due to retrieval of OR-based tasks, but not as a consequence of general behavioral procedures. Also, the pattern of activation was different in tasks with different cognitive demands. Taken together, the analyses of c-Fos and Zif-268 expressions suggest the activation of CA1 and DG hippocampal subregions, as well as PRh after what-where memory retrieval, while the standard OR task seems to involve mPFC, DG, and PRh areas. Accordingly, correlation tests suggest the engagement of different neural networks in the OR tasks used. Specifically, perirhinal-hippocampal co-activation was detected after the what-where memory retrieval, which correlated with the respective behavioral outcome. These findings can be helpful in the understanding of the neural networks underlying memory tasks with different cognitive demands.

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REFERENCES

Aggleton, J. P., and Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends Cogn. Sci. (Regul. Ed.)* 10, 455–463. doi:10.1016/j.tics.2006.08.003

Aggleton, J. P., Brown, M. W., and Albasser, M. M. (2012). Contrasting brain activity patterns for item recognition memory and associative recognition memory: insights from immediate-early gene functional imaging. *Neuropsychologia* 50, 3141–3155. doi:10.1016/j.neuropsychologia.2012.05.018

Ainge, J. A., Heron-Maxwell, C., Theofilas, P., Wright, P., de Hoz, L., and Wood, E. R. (2006). The role of the hippocampus in object recognition in rats: examination of the influence of task parameters and lesion size. *Behav. Brain Res.* 167, 183–195. doi:10.1016/j.bbr.2005.09.005

Albasser, M. M., Olarte-Sanchez, C. M., Amin, E., Horne, M. R., Newton, M. J., Warburton, E. C., et al. (2013). The neural basis of nonvisual object recognition memory in the rat. *Behav. Neurosci.* 127, 70–85. doi:10.1037/a0031216

Albasser, M. M., Poirier, G. L., and Aggleton, J. P. (2010). Qualitatively different modes of perirhinal-hippocampal engagement when rats explore novel vs. familiar objects as revealed by c-Fos imaging. *Eur. J. Neurosci.* 31, 134–147. doi:10.1111/j.1460-9568.2009.07042.x

Barbosa, F. F., de Oliveira Pontes, I. M., Ribeiro, S., Ribeiro, A. M., and Silva, R. H. (2012). Differential roles of the dorsal hippocampal regions in the acquisition of spatial and temporal aspects of episodic-like memory. *Behav. Brain Res.* 232, 269–277. doi:10.1016/j.bbr.2012.04.022

Barbosa, F. F., Pontes, I. M. D., Ribeiro, A. M., and Silva, R. H. (2010). Extending possible applications of an episodic-like memory task in rats. *Behav. Brain Res.* 215, 326–331. doi:10.1016/j.bbr.2009.11.028

Barker, G. R. I., Bird, F., Alexander, V., and Warburton, E. C. (2007). Recognition memory for objects, place, and temporal order: a disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex. *J. Neurosci.* 27, 2948–2957. doi:10.1523/JNEUROSCI.5289-06.2007

Barker, G. R. I., and Warburton, E. C. (2008). NMDA receptor plasticity in the perirhinal and prefrontal cortices is crucial for the acquisition of long-term object-in-place associative memory. *J. Neurosci.* 28, 2837–2844. doi:10.1523/JNEUROSCI.4447-07.2008

Barker, G. R. I., and Warburton, E. C. (2011). When is the hippocampus involved in recognition memory? *J. Neurosci.* 31, 10721–10731. doi:10.1523/JNEUROSCI.6413-10.2011

Bernabeu, R., Thiriet, N., Zwiller, J., and Di Scala, G. (2006). Lesion of the lateral entorhinal cortex amplifies odor-induced expression of c-fos, junB, and zif 268 mRNA in rat brain. *Synapse* 59, 135–143. doi:10.1002/syn.20224

Bisler, S., Schleicher, A., Gass, P., Stehle, J. H., Zilles, K., and Staiger, J. F. (2002). Expression of c-Fos, ICER, Krox-24 and JunB in the whisker-to-barrel pathway of rats: time course of induction upon whisker stimulation by tactile exploration of an enriched environment. *J. Chem. Neuroanat.* 23, 187–198. doi:10.1016/S0891-0618(01)00155-7

Bozon, B., Davis, S., and Laroche, S. (2002). Regulated transcription of the immediate-early gene Zif268: mechanisms and gene dosage-dependent function in synaptic plasticity and memory formation. *Hippocampus* 12, 570–577. doi:10.1002/hipo.10100

Bozon, B., Davis, S., and Laroche, S. (2003a). A requirement for the immediate early gene zif268 in reconsolidation of recognition memory after retrieval. *Neuron* 40, 695–701. doi:10.1016/S0896-6273(03)00674-3

Bozon, B., Kelly, A., Josselyn, S. A., Silva, A. J., Davis, S., and Laroche, S. (2003b). MAPK, CREB and zif268 are all required for the consolidation of recognition memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 805–814. doi:10.1098/rstb.2002.1224

Brown, M. W., and Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61. doi:10.1038/35049064

Castilla-Ortega, E., Pedraza, C., Chun, J., Rodriguez de Fonseca, F., Estivill-Torrus, G., and Santin, L. J. (2012). Hippocampal c-Fos activation in normal and LPA(1)-null mice after two object recognition tasks with different memory demands. *Behav. Brain Res.* 232, 400–405. doi:10.1016/j.bbr.2012.04.018

Chaudhuri, A., Zangenehpour, S., Rahbar-Dehgan, F., and Ye, F. (2000). Molecular maps of neural activity and quiescence. *Acta Neurobiol. Exp. (Wars.)* 60, 403–410.

Clayton, N. S., Bussey, T. J., and Dickinson, A. (2003). Can animals recall the past and plan for the future? *Nat. Rev. Neurosci.* 4, 685–691. doi:10.1038/nrn1180

Davis, S., Bozon, B., and Laroche, S. (2003). How necessary is the activation of the immediate early gene zif 268 in synaptic plasticity and learning? *Behav. Brain Res.* 142, 17–30. doi:10.1016/S0166-4328(02)00421-7

Davis, S., Bozon, B., Laroche, S., Garel, S., Charnay, P., Jones, M. W., et al. (2000). Zif268 is required for the stabilisation of LTP in the dentate gyrus and for two forms of learning. *Eur. J. Neurosci.* 12, 248–248.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2007). The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. *Neurosci. Biobehav. Rev.* 31, 673–704. doi:10.1016/j.neubiorev.2007.01.005

Dere, E., Huston, J. P., and Silva, M. (2005a). Integrated memory for objects, places, and temporal order: evidence for episodic-like memory in mice. *Neurobiol. Learn. Mem.* 84, 214–221. doi:10.1016/j.nlm.2005.07.002

Dere, E., Huston, J. P., and Silva, M. A. S. (2005b). Episodic-like memory in mice: simultaneous assessment of object, place and temporal order memory. *Brain Res. Protoc.* 16, 10–19. doi:10.1016/j.brainresprot.2005.08.001

Dere, E., Kart-Teke, E., Huston, J. P., and Silva, M. A. D. (2006). The case for episodic memory in animals. *Neurosci. Biobehav. Rev.* 30, 1206–1224. doi:10.1016/j.neubiorev.2006.09.005

DeVito, L. M., and Eichenbaum, H. (2010). Distinct contributions of the hippocampus and medial prefrontal cortex to the "what-where-when" components of episodic-like memory in mice. *Behav. Brain Res.* 215, 318–325. doi:10.1016/j.bbr.2009.09.014

DeVito, L. M., and Eichenbaum, H. (2011). Memory for the order of events in specific sequences: contributions of the hippocampus and medial prefrontal cortex. *J. Neurosci.* 31, 3169–3175. doi:10.1523/JNEUROSCI.4202-10.2011

Dix, S. L., and Aggleton, J. P. (1999). Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition. *Behav. Brain Res.* 99, 191–200. doi:10.1016/S0166-4328(98)00079-5

Eichenbaum, H., Yonelinas, A. P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152. doi:10.1146/annurev.neuro.30.051606.094328

Frankland, P. W., and Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130. doi:10.1038/nrn1607

Guzowski, J. F., Knierim, J. J., and Moser, E. I. (2004). Ensemble dynamics of hippocampal regions CA3 and CA1. *Neuron* 44, 581–584. doi:10.1016/j.neuron.2004.11.003

Herdegen, T., and Leah, J. D. (1998). Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Res. Brain Res. Rev.* 28, 370–490. doi:10.1016/S0165-0173(98)00018-6

Hoge, J., and Kesner, R. P. (2007). Role of CA3 and CA1 subregions of the dorsal hippocampus on temporal processing of objects. *Neurobiol. Learn. Mem.* 88, 225–231. doi:10.1016/j.nlm.2007.04.013

Hunsaker, M. R., Chen, V., Tran, G. T., and Kesner, R. P. (2013). The medial and lateral entorhinal cortex both contribute to contextual and item recognition memory: a test of the binding ofitems and context model. *Hippocampus* 23, 380–391. doi:10.1002/hipo.22097

Hunsaker, M. R., and Kesner, R. P. (2008). Evaluating the differential roles of the dorsal dentate gyrus, dorsal CA3, and dorsal CA1 during a temporal ordering for spatial locations task. *Hippocampus* 18, 955–964. doi:10.1002/hipo.20455

Hunsaker, M. R., Rosenberg, J. S., and Kesner, R. P. (2008). The role of the dentate gyrus, CA3a,b, and CA3c for detecting spatial and environmental novelty. *Hippocampus* 18, 1064–1073. doi:10.1002/hipo.20464

Jenkins, T. A., Amin, E., Pearce, J. M., Brown, M. W., and Aggleton, J. P. (2004). Novel spatial arrangements of familiar visual stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a c-fos expression study. *Neuroscience* 124, 43–52. doi:10.1016/j.neuroscience.2003.11.024

Jones, M. W., Errington, M. L., French, P. J., Fine, A., Bliss, T. V. P., Garel, S., et al. (2001). A requirement for the immediate early gene Zif268 in the expression of late LTP and long-term memories. *Nat. Neurosci.* 4, 289–296. doi:10.1038/85138

Kart-Teke, E., Dere, E., Brandao, M. L., Huston, J. P., and Silva, M. A. D. (2007). Reinstatement of episodic-like memory in rats by

neurokinin-1 receptor antagonism. *Neurobiol. Learn. Mem.* 87, 324–331. doi:10.1016/j.nlm.2006.09.007

Kart-Teke, E., Silva, M., Huston, J. P., and Dere, E. (2006). Wistar rats show episodic-like memory for unique experiences. *Neurobiol. Learn. Mem.* 85, 173–182. doi:10.1016/j.nlm.2005.10.002

Kealy, J., and Commins, S. (2011). The rat perirhinal cortex: a review of anatomy, physiology, plasticity, and function. *Prog. Neurobiol.* 93, 522–548. doi:10.1016/j.pneurobio.2011.03.002

Kesner, R. P. (2007). "A behavioral analysis of dentate gyrus function," in *Dentate Gyrus: A Comphrehensive Guide to Structure, Function, and Clinical Implications Progress in Brain Research*, Vol. 163, ed. H. Scharfman (Netherlands: Elsevier), 567–576.

Kim, J. J., Delcasso, S., and Lee, I. (2011). Neural correlates of object-in-place learning in hippocampus and prefrontal cortex. *J. Neurosci.* 31, 16991–17006. doi:10.1523/JNEUROSCI.2859-11.2011

Kubik, S., Miyashita, T., and Guzowski, J. F. (2007). Using immediate-early genes to map hippocampal subregional functions. *Learn. Mem.* 14, 758–770. doi:10.1101/lm.698107

Leon, W. C., Bruno, M. A., Allard, S., Nader, K., and Cuello, A. C. (2010). Engagement of the PFC in consolidation and recall of recent spatial memory. *Learn. Mem.* 17, 297–305. doi:10.1101/lm.1804410

Leutgeb, J. K., Leutgeb, S., Moser, M. B., and Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science* 315, 961–966. doi:10.1126/science.1135801

Li, J. S., and Chao, Y. S. (2008). Electrolytic lesions of dorsal CA3 impair episodic-like memory in rats. *Neurobiol. Learn. Mem.* 89, 192–198. doi:10.1016/j.nlm.2007.06.006

McClelland, J. L., McNaughton, B. L., and Oreilly, R. C. (1995). Why there are complementary learning-systems in the hippocampus and neocortex – insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457. doi:10.1037/0033-295X.102.3.419

Mumby, D. G., Gaskin, S., Glenn, M. J., Schramek, T. E., and Lehmann, H. (2002). Hippocampal damage and exploratory preferences in rats: memory for objects, places, and contexts. *Learn. Mem.* 9, 49–57. doi:10.1101/lm.41302

Norman, K. A., and O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychol. Rev.* 110, 611–646. doi:10.1037/0033-295X.110.4.611

Paxinos, G., and Watson, C. (2007). *The Rat Brain in Stereotaxic Coordinates*, 6th Edn. Oxford: Elsevier.

Rinaldi, A., Romeo, S., Agustin-Pavon, C., Oliverio, A., and Mele, A. (2010). Distinct patterns of Fos immunoreactivity in striatum and hippocampus induced by different kinds of novelty in mice. *Neurobiol. Learn. Mem.* 94, 373–381. doi:10.1016/j.nlm.2010.08.004

Soulé, J., Penke, Z., Kanhema, T., Alme, M. N., Laroche, S., and Bramham, C. R. (2008). Object-place recognition learning triggers rapid induction of plasticity-related immediate early genes and synaptic proteins in the rat dentate gyrus. *Neural Plast.* 2008, 269097. doi:10.1155/2008/269097

Squire, L. R., and Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13515–13522. doi:10.1073/pnas.93.24.13515

Treves, A., Tashiro, A., Witter, M. P., and Moser, E. I. (2008). What is the mammalian dentate gyrus good for? *Neuroscience* 154, 1155–1172. doi:10.1016/j.neuroscience.2008.04.073

Tulving, E. (2001). Episodic memory and common sense: how far apart? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1505–1515. doi:10.1098/rstb.2001.0937

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

van Strien, N. M., Cappaert, N. L. M., and Witter, M. P. (2009). The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network. *Nat. Rev. Neurosci.* 10, 272–282. doi:10.1038/nrn2614

VanElzakker, M., Fevurly, R. D., Breindel, T., and Spencer, R. L. (2008). Environmental novelty is associated with a selective increase in Fos expression in the output elements of the hippocampal formation and the perirhinal cortex. *Learn. Mem.* 15, 899–908. doi:10.1101/lm.1196508

Wan, H., Warburton, E. C., Kusmierek, P., Aggleton, J. P., Kowalska, D. M., and Brown, M. W. (2001). Fos imaging reveals differential neuronal activation of areas of rat temporal cortex by novel and familiar sounds. *Eur. J. Neurosci.* 14, 118–124. doi:10.1046/j.0953-816x.2001.01625.x

Wan, H. M., Aggleton, J. P., and Brown, M. W. (1999). Different contributions of the hippocampus and perirhinal cortex to recognition memory. *J. Neurosci.* 19, 1142–1148.

Winters, B. D., and Bussey, T. J. (2005a). Glutamate receptors in perirhinal cortex mediate encoding, retrieval, and consolidation of object recognition memory. *J. Neurosci.* 25, 4243–4251. doi:10.1523/JNEUROSCI.0480-05.2005

Winters, B. D., and Bussey, T. J. (2005b). Transient inactivation of perirhinal cortex disrupts encoding, retrieval, and consolidation of object recognition memory. *J. Neurosci.* 25, 52–61. doi:10.1523/JNEUROSCI.0480-05.2005

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Memories of the future: new insights into the adaptive value of episodic memory

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Ingvar (1979, p. 21) theorized that memory plays a key role in allowing individuals to construct "alternative hypothetical behavior patterns in order to be ready for what may happen," a process that he characterized as a "simulation of behavior". Several years later, Ingvar elaborated these ideas by observing that "concepts about the future, like memories of past events, can be remembered, often in great detail" (Ingvar, 1985, p. 128), and that such "memories of the future" may offer important insights into the adaptive nature of human cognition. For instance, although the ability to simulate alternative versions of the future can benefit behavior, at least part of the adaptive advantage of future thinking may depend on the ability to remember the contents of simulated events (for discussion, see Suddendorf and Corballis, 1997, 2007; Szpunar, 2010; Schacter, 2012; Schacter et al., 2012). As an example, enlisting mental simulations of the future to help determine the best approach for resolving a conflict at home or in the workplace may confer few advantages if the outcome of the simulation process is not remembered at the time the simulated behavior is executed. Although much research exists concerning prospective memory – remembering to carry out future intentions (e.g., Kliegel et al., 2008; see also Brewer and Marsh, 2009) – there is a striking lack of evidence concerning "memory of the future" in the sense discussed by Ingvar, that is, memory for the contents of future simulations. Recently, however, several studies have provided the first glimpses into how well people remember details associated with simulated future events. In particular, these studies have demonstrated (1) enhanced memory for event details that are encoded with the future in mind, (2) factors that may influence the retention of simulated future events over extended time periods, and (3) neural correlates associated with encoding simulated future events. Next, we provide a brief overview of this emerging line of research, underscore the significance of various findings along with suggestions for future research directions, and conclude by discussing the relevance of this work to the concept of episodic memory. As we expand on below, it is our opinion that these new studies represent not only a useful extension of Ingvar's (1979, 1985) seminal observations, but that they also offer novel insights into the adaptive value of episodic memory.

FUTURE-ORIENTED ENCODING PROCESSES ENHANCE RETENTION

Klein et al. (2012, p. 240) have recently noted that systems of memory, including episodic memory, may be "designed by evolution to interface with systems of long-term planning" (see also Suddendorf and Corballis, 2007). Accordingly, memory systems should be more efficient in dealing with encoding manipulations that encourage future-oriented processes such as planning than other well-established encoding manipulations that are not necessarily oriented toward the future (e.g., imagery, self-relevance; see also Klein et al., 2002; Klein et al., 2010; McDonough and Gallo, 2010). A recent line of research supports this prediction. Klein et al. (2010) asked separate groups of participants to think about one of three camping scenarios: imagining a future camping trip, remembering a past camping trip, or imagining a typical campsite without reference to the past or future. During the simulation/retrieval task, participants were asked to indicate how likely it was that various items (e.g., tent, rope) were incorporated into their self-generated scenarios. After a brief delay, participants were presented with a blank sheet of paper and asked to recall the list of items associated with the simulation/retrieval task. Participants who had simulated a future camping trip remembered more items than participants who had remembered a camping trip or simulated a typical campsite in an atemporal manner.

Notably, Klein et al. (2010) included a fourth encoding condition that asked a separate group of participants to imagine a hypothetical camping scenario in which they were stranded in a forest, and to indicate how likely it was that the same set of items (e.g., tent, rope) would enhance their chances of survival. This latter condition was included in response to a recent series of studies by Nairne and colleagues demonstrating that attending to the survival value of to-be-encoded information also enhances retention relative to other well-established encoding manipulations (for a review, see Nairne, 2010). Klein et al. (2010) hypothesized that survival processing may enhance retention to the extent that it calls upon future-oriented processes such as planning. Along these lines, Klein et al. (2010) further suggested that the survival scenario might evoke planning in some participants but not others; for instance, some participants may think about the survival scenario in an atemporal manner. Hence, while details associated with the survival

scenario should be better remembered than details associated with scenarios that do not evoke planning (e.g., remembering a camping trip), details associated with the survival scenario should not be remembered as well as details associated with scenarios that always evoke planning (e.g., imagining a future camping trip). Klein et al. (2010) found support for both of these predictions. In a subsequent study, Klein et al. (2011) systematically varied the involvement of planning and survival processing in various simulated scenarios, and found that participants were better able to remember details associated with scenarios that had evoked planning, whether or not survival processing was relevant, than details associated with survival scenarios that had not evoked planning.

Nonetheless, some studies have failed to demonstrate a mnemonic advantage for encoding conditions that foster planning as compared to survival processing (e.g., Kang et al., 2008; Weinstein et al., 2008). In response to these incongruent findings, Klein et al. (2010, 2011) pointed out that enhanced memory for plans might depend on the extent to which plans evoke concepts of the personal future, such as planning for events that participants have experienced in the past and expect to experience again in the future. To test this claim, Klein et al. (2012) asked separate groups of participants to plan for familiar (e.g., dinner party) and unfamiliar (e.g., trip to Antarctica) scenarios. Participants who had made plans for familiar scenarios remembered more details associated with those scenarios than participants who had made plans for unfamiliar scenarios.

Hence, the available evidence suggests that people are rather adept at encoding and subsequently remembering details about simulated future events. We conclude this section by discussing a recent study demonstrating how enhanced memory for details associated with future events can be used to help people distinguish between memories of the past and future. Earlier research on the relation between memory and imagination had demonstrated that memories and simulated events are best characterized by distinct phenomenological features: remembered events tend to be characterized by enhanced perceptual clarity whereas imagined events tend to be characterized by increased representation of cognitive operations (for a review, see Johnson, 1988). Building on the results of Johnson and others, McDonough and Gallo (2010) found that people were able to make use of phenomenological characteristics such as perceptual clarity and cognitive operations when discriminating between memories of past and future events. Interestingly, the authors also found that the distinguishing characteristics of future events – cognitive operations – were more diagnostic in discriminating between memories of past and future events than were the distinguishing characteristics of memories – perceptual clarity. Accordingly, McDonough and Gallo (2010) noted that this latter pattern of results might reflect the workings of a memory system whose primary function involves "imagination and planning for future events" (p. 7).

In sum, the results of a number of studies have demonstrated that encoding manipulations that encourage future-oriented processes such as planning improve retention relative to other well-established encoding manipulations. Moving forward, studies that can identify the possible factors that underlie the mnemonic advantage associated with future-oriented encoding processes, such as the role of familiarity and personal experience (Klein et al., 2012), will be of considerable interest. As an initial step in that direction, McLelland et al. (submitted) identified several event characteristics that predicted the likelihood of successful encoding of future events. Imagined future events that were rated by participants as being more detailed, more plausible, and involving more familiar elements (in particular, events with more familiar people) were all significantly more likely to be later remembered than imagined events with low ratings on such characteristics.

RETENTION OF SIMULATED FUTURE EVENTS OVER EXTENDED PERIODS

In the studies discussed thus far, memory for future simulations was tested after relatively brief study-test delays (usually 5–20 min post simulation). Yet in the everyday situations discussed by Ingvar (1985), it may be necessary to retain a simulation over days and weeks. However, only two studies of which we are aware have examined memory for simulated future events at extended delays. In one study, Szpunar et al. (2012) asked participants to imagine future scenarios comprising people, locations, and objects that had been extracted from autobiographical memories or participant-generated lists. Memory for simulations was tested either shortly after simulation (20 min) or after an extended delay (24 h) by providing two elements of the simulated episode (e.g., person and object) and probing for recall of the third element (e.g., location). Interestingly, more emotional simulations (i.e., positive and negative events) were remembered than neutral simulations after the short delay, whereas more positive and neutral simulations were remembered than negative simulations after the long delay. That is, negative simulations were forgotten more quickly than positive and neutral simulations. This pattern of data may reflect the influence of fading affect bias (Walker and Skowronski, 2009), such that the affect that binds event details together (Mather and Sutherland, 2011) may dissipate more quickly for negative than positive events. Notably, Gallo et al. (2011) also found a positivity bias in memory for simulated future events after 24 h in young and old adults. Hence, the available data suggests that people may remember a rosy simulated future. Further studies of memory for simulated emotional events may thus have the potential to provide insights into various mood disorders such as anxiety and depression.

NEURAL SUBSTRATES FOR ENCODING SIMULATIONS OF FUTURE EVENTS

So far, studies concerning "memory of the future" have focused mainly on cognitive processes. Although little is known about the neural processes that support encoding of simulated future events, a recent study by Martin et al. (2011) indicates that the hippocampus plays an important role. During fMRI scanning, participants imagined future scenarios comprising people, locations, and objects that were extracted from autobiographical memories. Memory for simulations was tested shortly after the scan by providing two elements of the simulated episode (e.g., person and object) and probing for recall of the third element (e.g., location); a simulation was classified as "remembered" when participants recalled the third element correctly, and "forgotten" when they did not. Greater hippocampal activity was observed during construction of subsequently remembered than forgotten

simulations even when controlling for the amount of detail associated with each simulation (for discussion of related findings, see Addis and Schacter, 2012; Schacter et al., 2012). Looking ahead, studies will be needed that can isolate the neural circuitry that underlies the mnemonic advantage produced by encoding information with the future in mind.

SUMMARY AND CONCLUSIONS

Over the last four decades, the concept of episodic memory has evolved into a multifaceted construct that is of great interest to researchers in various areas of psychology and neuroscience (for recent overviews, see Szpunar and McDermott, 2008; Tulving and Szpunar, 2009). Here, we have highlighted recent insights into an adaptive feature of episodic memory first noted by Ingvar (1985): "memories of the future," like memories of past events, can help to guide behavior. Given the potential theoretical and practical importance of understanding memories of the future, it is perhaps surprising that so little relevant experimental work has been done. Developing a more in depth understanding of why simulated future events are well remembered, what factors influence the long-term retention of simulated future events, and how the brain supports the encoding of simulated future events, represent important avenues for future research that are likely to broaden our understanding of the utility of episodic memory in everyday life.

REFERENCES

Addis, D. R., and Schacter, D. L. (2012). The hippocampus and imagining the future: where do we stand? *Front. Hum. Neurosci.* 5:173. doi: 10.3389/fnhum.2011.00173

Brewer, G. A., and Marsh, R. L. (2009). On the role of episodic future simulation in encoding of prospective memories. *Cogn. Neurosci.* 1, 81–88.

Gallo, D. A., Korthauer, L. E., McDonough, I. M., Teshale, S., and Johnson, E. L. (2011). Age-related positivity effects and autobiographical memory detail: evidence from a past/future source memory task. *Memory* 19, 641–652.

Ingvar, D. H. (1979). "Hyperfrontal" distribution of the cerebral grey matter flow in resting wakefulness: on the functional anatomy of the conscious state. *Acta Neurol. Scand.* 60, 12–25.

Ingvar, D. H. (1985). "Memory of the future": an essay on the temporal organization of conscious awareness. *Hum. Neurobiol.* 4, 127–136.

Johnson, M. K. (1988). Reality monitoring: an experimental phenomenological approach. *J. Exp. Psychol. Gen.* 117, 390–394.

Kang, S. H. K., McDermott, K. B., and Cohen, S. M. (2008). The mnemonic advantage of processing fitness-relevant information. *Mem. Cognit.* 36, 1151–1156.

Klein, S. B., Cosmides, L., Tooby, J., and Chance, S. (2002). Decisions and the evolution of memory: multiple systems, multiple functions. *Psychol. Rev.* 109, 306–329.

Klein, S. B., Robertson, T. E., and Delton, A. W. (2010). Facing the future: memory as an evolved system for planning future acts. *Mem. Cognit.* 38, 13–22.

Klein, S. B., Robertson, T. E., and Delton, A. W. (2011). The future-orientation of memory: planning as a key component mediating the high levels of recall found with survival processing. *Memory* 19, 121–139.

Klein, S. B., Robertson, T. E., Delton, A. W., and Lax, M. L. (2012). Familiarity and personal experience as mediators of recall when planning for future contingencies. *J. Exp. Psychol. Learn. Mem. Cogn.* 38, 240–245.

Kliegel, M., McDaniel, M. A., and Einstein, G. O. (2008). *Prospective Memory: Cognitive, Neuroscience, Developmental, and Applied Perspectives.* Mahwah, NJ: Erlbaum.

Martin, V. C., Schacter, D. L., Corballis, M. C., and Addis, D. R. (2011). A role for the hippocampus in encoding simulations of future events. *Proc. Natl. Acad. Sci. U.S.A.* 108, 13858–13863.

Mather, M., and Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.* 6, 114–133.

McDonough, I. M., and Gallo, D. A. (2010). Separating past and future autobiographical events in memory: evidence for a reality monitoring asymmetry. *Mem. Cognit.* 38, 3–12.

Nairne, J. S. (2010). "Adaptive memory: evolutionary constraints on remembering," in *The Psychology of Learning and Motivation*, ed. B. H. Ross (London: Academic Press), 1–32.

Schacter, D. L. (2012). Adaptive constructive processes and the future of memory. *Am. Psychol.* 67, 603–613.

Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., and Szpunar, K. K. (2012). The future of memory: remembering, imagining, and the brain. *Neuron* 76, 677–694.

Suddendorf, T., and Corballis, M. C. (1997). Mental time travel and the evolution of the human mind. *Genet. Soc. Gen. Psychol. Monogr.* 123, 133–167.

Suddendorf, T., and Corballis, M. C. (2007). The evolution of foresight: what is mental time travel, and is it unique to humans? *Behav. Brain Sci.* 30, 299–313.

Szpunar, K. K. (2010). Episodic future thought: an emerging concept. *Perspect. Psychol. Sci.* 5, 142–162.

Szpunar, K. K., Addis, D. R., and Schacter, D. L. (2012). Memory for emotional simulations: remembering a rosy future. *Psychol. Sci.* 23, 24–29.

Szpunar, K. K., and McDermott, K. B. (2008). "Episodic memory: an evolving concept," in *Cognitive Psychology of Memory, Vol. 2 of Learning and Memory: A Comprehensive Reference*, eds H. L. Roediger and J. H. Byrne (Oxford: Elsevier), 491–509.

Tulving, E., and Szpunar, K. K. (2009). Episodic memory. *Scholarpedia* 4, 3332.

Walker, W. R., and Skowronski, J. J. (2009). The fading affect bias: but what the hell is it for? *Appl. Cogn. Psychol.* 23, 1122–1136.

Weinstein, Y., Bugg, J. M., and Roediger, H. L. (2008). Can the survival recall advantage be explained by basic memory processes? *Mem. Cognit.* 36, 913–919.

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The pivotal role of semantic memory in remembering the past and imagining the future

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Episodic memory refers to a complex and multifaceted process which enables the retrieval of richly detailed evocative memories from the past. In contrast, semantic memory is conceptualized as the retrieval of general conceptual knowledge divested of a specific spatiotemporal context. The neural substrates of the episodic and semantic memory systems have been dissociated in healthy individuals during functional imaging studies, and in clinical cohorts, leading to the prevailing view that episodic and semantic memory represent functionally distinct systems subtended by discrete neurobiological substrates. Importantly, however, converging evidence focusing on widespread neural networks now points to significant overlap between those regions essential for retrieval of autobiographical memories, episodic learning, and semantic processing. Here we review recent advances in episodic memory research focusing on neurodegenerative populations which has proved revelatory for our understanding of the complex interplay between episodic and semantic memory. Whereas episodic memory research has traditionally focused on retrieval of autobiographical events from the past, we also include evidence from the recent paradigm shift in which episodic memory is viewed as an adaptive and constructive process which facilitates the imagining of possible events in the future. We examine the available evidence which converges to highlight the pivotal role of semantic memory in providing schemas and meaning whether one is engaged in autobiographical retrieval for the past, or indeed, is endeavoring to construct a plausible scenario of an event in the future. It therefore seems plausible to contend that semantic processing may underlie most, if not all, forms of episodic memory, irrespective of temporal condition.

Keywords: semantic dementia, autobiographical memory, future thinking, Alzheimer's disease, episodic memory, anterior temporal lobes, semantic memory

INTRODUCTION

One of the most fascinating aspects of human cognition is our ability to withdraw from the current moment and to mentally transport ourselves to another time, place, or perspective. Collectively, the abilities to remember the past via episodic autobiographical memory (ABM), or to imagine possible future events, represent important expressions of the human memory system (Tulving, 2002), potentially conferring a significant adaptive advantage in planning for the future (Suddendorf and Corballis, 2007; Klein, 2013). In recent years, episodic memory has been reconceptualized as not only the capacity for retrieval from our personal past, but also encompassing the ability to imagine and envisage possible future scenarios, leading to a constructivist view on how humans might achieve such sophisticated acts of cognition (Hassabis and Maguire, 2007; Schacter and Addis, 2007a). Neuroimaging studies have uncovered a widespread "core" network which subtends the successful retrieval of autobiographical memories from our past (Maguire, 2001; Svoboda et al., 2006; Cabeza and St. Jacques, 2007; Schacter et al., 2007). Importantly, this core network includes frontal and medial temporal regions, notably the hippocampus, lateral temporal, sensory association cortices, and more posterior parietal regions (Spreng et al., 2009), reflecting the multifaceted nature of this type of memory (see **Figure 1**). While considerable variation exists in the classification of episodic memory, in this article, we refer to the contents of episodic memory as "remembered experiences," or ABM (see Tulving and Szpunar, 2009). As will become evident, however, the contents of episodic memory invariably involve semantic representations.

In contrast to the largely evocative, spatiotemporally specific, and often emotionally charged, instances of episodic memories from the past sits the repository of all acquired atemporal knowledge of the world, semantic memory. Traditionally, the episodic/semantic distinction has served as a useful heuristic within the neuropsychological literature (Greenberg and Verfaellie, 2010), underscoring the importance of the medial temporal lobes, specifically the hippocampus, in the encoding and retrieval of episodic memories in contrast with the centrality of the anterior temporal lobes for the retrieval of semantic information. Similar to episodic memory, semantic memory is viewed as essential for many aspects of cognition, including language, reasoning,

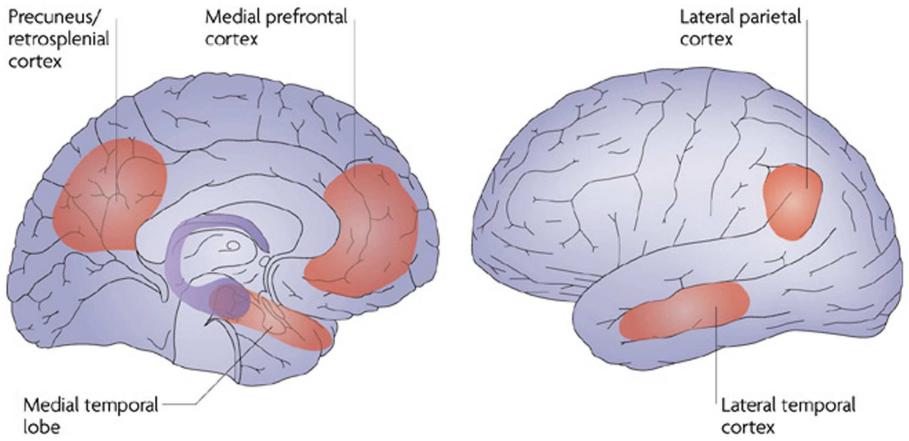


FIGURE 1 | Component structures of the core memory network consistently activated during autobiographical retrieval of the past, and constructive simulation of the future. Notably, the lateral temporal cortex is implicated across past and future contexts, highlighting the central role for semantic memory in past and future oriented thought. Reprinted by permission from Macmillan Publishers Ltd., Schacter et al. (2007). Copyright (2007).

planning, problem-solving, and social interaction (Binder et al., 2009). In support of this position, neuroimaging studies have demonstrated significant activation in semantic processing regions in healthy individuals across a wide variety of cognitive abilities including distinguishing real from fictitious scenarios (Abraham et al., 2008a), positive counterfactual thinking (Van Hoeck et al., in press), as well as engaging in processes relevant for creativity (Vartanian, 2012). In contrast to the spatiotemporal specificity of episodic memory, semantic memory is derived from the abstraction of content from experiences, which is represented using modality-specific simulations whereby information relevant to a specific mode of experience is processed within the corresponding sensory, motor, or affective system (Binder and Desai, 2011). These representations are processed, therefore, in high level supramodal convergence zones in the brain including the inferior parietal cortex, the middle and inferior temporal gyri, and anterior portions of the fusiform gyrus (Patterson et al., 2007; Binder et al., 2009; Binder and Desai, 2011). Importantly, the semantic system recently identified in a meta-analysis of 120 functional neuroimaging studies exhibits striking overlap to the large-scale core ABM network (Maguire, 2001; Svoboda et al., 2006; Binder et al., 2009) prompting the observation that autobiographical memories necessarily contain a high level of semantic concepts (Binder et al., 2009), and that, by its nature, semantic representations are essential for a host of complex cognitive functions including remembering the past and imaging the future (Binder and Desai, 2011). These recent proposals resonate with mounting evidence from the neuroimaging literature demonstrating considerable overlap between episodic and semantic memory systems and the unclear boundaries that exist between these forms of memory (Burianova et al., 2010).

With the advent of sophisticated neuroimaging techniques, we have witnessed a shift in perspective from studying specific brain structures in isolation to the consideration of carefully orchestrated neural networks. Converging evidence now points to the role of large-scale neural networks in subtending complex cognitive processes, and the intriguing possibility that semantic processing may play a central role in all aspects of internal mentation.

THE STUDY OF NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders offer a compelling view of the cognitive architecture of the brain when specific neural systems break down in a coordinated fashion (Irish et al., 2012c). In this review, we will focus on Alzheimer's disease (AD) and semantic dementia (SD) as lesion models for episodic and semantic memory processes, respectively, to demonstrate how these dementia syndromes illuminate our understanding of the complexity of the episodic memory system, and crucially, how episodic and semantic memory invariably interact during complex forms of past and future oriented thought.

Alzheimer's disease has long been heralded as a suitable lesion model for episodic memory processes, in light of the characteristic medial temporal lobe neural degeneration evident from a very early stage in the pathological process (Butters et al., 1987; Braak and Braak, 1991). Recent studies point to the preferential accumulation of amyloid deposits in specific nodes of the core ABM network in AD, most notably the posterior cingulate cortex and the anteromedial prefrontal cortex (Buckner et al., 2008). Clinically, AD patients typically present with an amnestic profile in which anterograde episodic memory difficulties concerning the encoding and retrieval of recent events are prominent (de Toledo-Morrell et al., 2000; McKhann et al., 2011). This disruption to episodic memory emerges as a consequence of the neuropathological process (neurofibrillary tangles and amyloid deposition), which affects the entorhinal cortex and hippocampus of the medial temporal lobes, and spreads to the neocortex (Ewers et al., 2011; Sperling et al., 2011). Importantly, such episodic memory deficits occur in the context of a relative sparing of semantic processing in the early stages of the disease (see **Table 1**).

The neurodegenerative disorder of SD represents the other side of the coin, in that the hallmark clinical feature of this disease concerns the progressive and amodal loss of semantic or general

Table 1 | Clinical characteristics of semantic dementia and Alzheimer's disease.

	Semantic dementia (SD)	Alzheimer's disease (AD)
Predominant brain atrophy	Lateral temporal Left > Right	Medial temporal Bilateral
Cognition[a]		
Executive function	Intact	+ – ++
Orientation	Intact	++
Recent episodic memory	Intact[b]	+++
Remote episodic memory	+++	+
Semantic knowledge	+++	±
Word comprehension	+++	±

[a] *Functions are relatively intact in the early stages of the disease;* [b] *contingent on the nature of test materials used; +, mild deficits; ++, moderate deficits; +++, severe deficits; ±, variable deficits.*

conceptual knowledge of the world (Hodges and Patterson, 2007). This loss of world knowledge occurs irrespective of modality and is theoretically attributable to the deterioration of a central amodal semantic hub (Rogers et al., 2004; Patterson et al., 2007; but, see Mesulam et al., 2013). On a neural level, SD is characterized by the progressive degeneration of the anterior temporal lobes (Hodges and Patterson, 2007), most severe on the ventral surface and including the perirhinal cortex, anterior fusiform gyrus (Whitwell et al., 2005; Mion et al., 2010), and typically lateralized to the left more than the right hemisphere. Importantly, volumetric MRI studies have confirmed that the degree of hippocampal atrophy in SD is equivalent, or greater, to that seen in disease-matched cases of AD, albeit in the context of much more severe temporal lobe atrophy (Chan et al., 2001; Galton et al., 2001). Of paramount importance in the current context, however, is the observation that despite profound semantic deficits, SD patients nevertheless display otherwise relatively preserved cognitive functions, including retrieval of recent episodic information, particularly when non-verbal tasks are employed (see **Table 1**; Bozeat et al., 2000; Crutch and Warrington, 2002; Hodges and Patterson, 2007).

In summary, the neurodegenerative disorders of AD and SD offer a unique opportunity to disentangle the interaction between the episodic and semantic memory systems. A theoretically important distinction is evident: while in AD we see the loss of episodic memory in the context of medial temporal lobe degeneration and relative preservation of semantic knowledge, in SD, the amodal deterioration of semantic memory occurs in the context of relatively preserved recent episodic memory. A range of interdependencies between episodic and semantic memory have recently been expounded (Greenberg and Verfaellie, 2010). Here, however, we will constrain our focus to explore how these dementia syndromes inform our understanding of two putative expressions of the episodic memory system, namely autobiographical retrieval of the past, and simulation of the future.

REMEMBERING THE PAST – AUTOBIOGRAPHICAL MEMORY

Perhaps the most important advances in understanding the interplay between episodic and semantic elements stem from the domain of ABM. The recollection of personal past memories from across our subjective timeline represents a powerful expression of the episodic memory system, requiring the retrieval of sensory-perceptual details, and emotional connotations, integrated within a specific spatiotemporal and personally relevant framework (Conway et al., 2004). Unsurprisingly, this complex endeavor is subtended by a distributed neural network involving the medial temporal lobes including the hippocampus and parahippocampal gyrus, the frontal poles, and more posterior regions including the posterior cingulate and parietal cortices, as well as the lateral temporal cortices (Maguire, 2001; Addis et al., 2004; Svoboda et al., 2006). It is noteworthy that across studies of ABM retrieval, activation of the lateral temporal cortices, regions known to be essential for semantic memory (Mion et al., 2010), is reliably observed (Spreng et al., 2009), suggesting a fundamental role for semantic processing underlying all forms of episodic past retrieval (see **Figure 1**).

PRESERVATION OF REMOTE ABMs IN ALZHEIMER'S DISEASE

The main structures implicated in ABM retrieval are those regions harboring significant atrophy in AD and SD. Importantly, our understanding of the neurocognitive mechanisms of ABM retrieval has been advanced from studying how the characteristic patterns of atrophy in AD and SD impact on the capacity for ABM retrieval. Little doubt exists regarding the prominent deficits in ABM typically seen in AD from early in the disease course. Irrespective of measure used, patients with AD demonstrate striking impairments, particularly on event or episodic subscales of these measures, in contrast with a relative preservation of personal semantics, at least in the early stages of the disease (Barnabe et al., 2012). A central debate in the ABM literature concerns the temporal profile of the episodic ABM deficit in AD, and specifically whether it conforms to Ribot's law (Ribot, 1881), in which memories from more distant time periods appear relatively intact. A number of early studies of ABM have demonstrated a disproportionate impairment of recent compared to remote episodic memories in AD (Kopelman et al., 1989; Greene et al., 1995; Graham and Hodges, 1997; Eustache et al., 2004; Irish et al., 2006, 2011b; Leyhe et al., 2009), which in turn has been interpreted in favor of a time-limited role of the hippocampus in long-term retrieval (Squire and Alvarez, 1995). The preservation of remote memories in AD, however, is of interest if we consider that older memories are more likely to undergo a process of semanticization (Cermak, 1984), leading to overgeneral memories that are divested of rich episodic re-experiencing (Irish et al., 2008, 2011b). The relative sparing of the lateral temporal cortices, and a reasonably intact capacity for reminiscence in remote epochs of one's life, in the early stages of AD accords with observations of reliance on gist memory in this syndrome (Gallo et al., 2006) and suggests that patients may overly depend on semantic representations of formerly episodic events. Similarly, patients with AD have been shown

to lose access to sensory-perceptual details and appear particularly deficient in evoking specific self-referential visual imagery during ABM retrieval (Irish et al., 2011b). This loss of visual imagery may preclude the triggering of an emotional response (Kosslyn et al., 2001) and disrupts the overall re-experiencing of the retrieved event. A recent study has demonstrated that the capacity to generate complex visual imagery is compromised in AD, with the proposal that such deficits may impinge upon the envisaging of oneself across past and future contexts (Hussey et al., 2012). Thus, for AD patients, the retrieval of a past event occurs in the absence of vivid visual imagery, producing overgeneral and depersonalized or semanticized accounts of the formerly evocative event. These categories of events can be subsumed under Neisser's concept of "repisodes" (Neisser, 1981), Barsalou's "extended events" (Barsalou, 1988), or Conway's view of "general events" within the ABM system (Conway, 2001; Greenberg and Verfaellie, 2010). While Irish et al. (2011b) reported a loss of self-referential visual imagery during retrieval of specific episodic autobiographical memories, the ability of AD patients to visualize repeated or abstracted experiences remains to be established. This represents an interesting, but underexplored area of research that has obvious relevance for the constructs under consideration.

Recent studies, including a large study from our group, have failed to demonstrate temporal gradients during ABM retrieval in AD (Piolino et al., 2003; Irish et al., 2011a). Such conflicting results may reflect differences in probing and scoring of ABMs across experimental protocols (Barnabe et al., 2012). Importantly, the separation of internal "episodic," from external, or non-episodic, details using the Autobiographical Interview (AI; Levine et al., 2002) in the Irish et al. (2011a) study, serves to constrain the focus to purely episodic recall in AD. While this approach has proved extremely useful for studying strictly episodic components of ABM narratives, the resultant flat profiles in AD are also revelatory in this context. The disappearance of temporal gradients during ABM retrieval, following the parsing of semantic from episodic details, suggests that semantic knowledge represents a sizeable proportion of remote memory content in AD. This observation meshes well with the view that the episodic and semantic memory systems are invariably interlinked (Greenberg and Verfaellie, 2010), and that episodic memory requires binding of contextual elements within existing frameworks of conceptual knowledge (Reder et al., 2009). The characteristic loss of episodic memory, thus prompts the AD patient to sample intact semantic and gist-based knowledge to guide their retrieval effort, as this approach represents the most accessible and efficient route of access (Greenberg and Verfaellie, 2010; Szpunar, 2010a).

AUTOBIOGRAPHICAL MEMORY RETRIEVAL IN SEMANTIC DEMENTIA

The investigation of profiles of ABM in SD has elucidated the impact of progressive semantic memory deterioration on episodic memory retrieval. Studies of ABM in SD have yielded inconsistent results, with most pointing to the converse profile to that characteristically seen in AD, namely a reverse temporal gradient, or more accurately, a step function (Hodges and Graham, 2001). The step function describes the observation of relatively preserved recent period retrieval in contrast with impairments in the recollection of memories from more remote epochs (Graham and Hodges, 1997; Nestor et al., 2002; Piolino et al., 2003; Hou et al., 2005; Matuszewski et al., 2009; Irish et al., 2011a; see **Figure 2**). The precise underpinnings of relatively intact recent period retrieval in SD remain contentious. This effect has been interpreted as reflecting preserved anterograde processes and encoding and retrieval mechanisms (Adlam et al., 2009; Matuszewski et al., 2009). Further, it has been suggested that recent memories encompass more sensory-perceptual elements rather than overgeneral or semanticized information (Hodges and Graham, 2001; Nestor et al., 2002), with SD patients relying on such perceptual features for recent retrieval. The step function profiles of ABM in SD offer further insights into the possible semanticization of episodic memories with repeated rehearsal and the passing of time. The repeated recollection and rehearsal of remote memories allows for the abstraction of the gist of the episode without its accompanying sensory-perceptual details (Rosenbaum et al., 2001), resulting in a largely schematic account of the formerly evocative event. By this view, remote memory deficits in SD reflect a loss of semantic information that is integral to the memory trace (Westmacott et al., 2001). Interestingly, McKinnon et al. (2008) reported an elevation of external (non-episodic) details in concert with a reduction in internal (episodic) details during ABM retrieval in SD. This effect was interpreted as reflecting a relative sparing of generic autobiographical information as well as the provision of tangential details. Thus, while the deterioration of semantic knowledge impinges on the capacity for successful ABM retrieval in SD, semantic elements relevant to the retrieved event are often present within the patients' ABM narratives. Notably, the ability to retrieve personal semantic and overgeneral autobiographical information from their past appears relatively preserved in SD (Greenberg and Verfaellie, 2010).

It should be noted, however, that a number of studies have failed to replicate the step function during ABM retrieval in SD (Westmacott et al., 2001; Moss et al., 2003; McKinnon et al., 2006; Maguire et al., 2010a). Such inconsistencies in the literature may stem from the methods used to probe ABM retrieval. It is notable that these

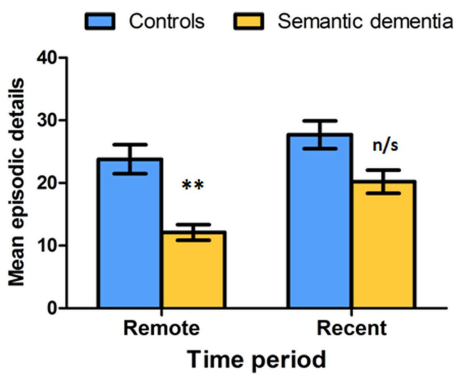


FIGURE 2 | Differential impairment of remote versus recent autobiographical memory in semantic dementia compared to healthy controls during free recall on the Autobiographical Interview (AI). Error bars represent standard error of the mean. $^{**}P < 0.0001$; n/s, not significant. Data adapted from Irish et al. (2011a).

studies all used non-verbal stimuli, such as family photographs, to elicit ABMs. Importantly, the use of non-verbal stimuli in SD tends to produce a flat profile, with recent and remote memories recalled equally well (Westmacott et al., 2001; Moss et al., 2003; Maguire et al., 2010a; Greenberg et al., 2011). This finding resonates with the proposal that SD patients may harness perceptual features of such visual cues to bypass their profound verbal and language impairments, enabling them to access sensory-perceptual details at a higher level in the ABM system (Conway, 2001; Nestor et al., 2002). The accessibility of perceptual details represents a plausible mechanism underlying preserved recent memory, given that SD patients demonstrate an intact capacity to retrieve sensory-perceptual details during recent, but not remote, ABM retrieval (Irish et al., 2011a), and have been shown to perform normally on sensory-perceptual processing tasks, at least, when feature ambiguity is low (Barense et al., 2010). Critically, the salience of ABMs in SD following the provision of such non-verbal cues speaks to the nature of the interdependence between semantic memory and ABM. When SD patients attempt to retrieve a remote event during traditional verbally loaded ABM tasks, their ability to access relevant perceptual details is hampered by their severe semantic impairment, with the ABM search terminating at the level of non-specific episodes or repeated events in the ABM system (Conway, 2001). Evidence from the domain of ABM therefore underscores the proposition that semantic memories form the basic foundation necessary for retrieval of complex and detailed episodic memories (Greenberg and Verfaellie, 2010). Of note, the Serial-Parallel-Independent (SPI) model proposed by Tulving (1995) has long held that information first enters episodic memory via semantic memory. This model resonates with our view emphasizing the interdependence between these memory systems, and accords with studies demonstrating that impairment in the semantic framework adversely affects the acquisition of new episodic memories in the verbal modality (Ween et al., 1996; Graham et al., 2000). In concert with the progressive deterioration of semantic memory in SD, we see the gradual erosion of episodic ABMs (Maguire et al., 2010a). Collectively, these findings reinforce the view that ABMs necessarily contain, and may critically rely upon, abstracted, supramodal representations of perceptual experiences, which in turn support the sophisticated act of self-projection backwards in time to remember the past (Binder and Desai, 2011; Irish et al., 2012c).

The evidence reviewed here indicates that semantic concepts form an integral component of episodic autobiographical memories, and accords with the conceptualization of autobiographical and semantic memory as opposite ends of a contextual continuum (Kihlstrom, 1984; Burianova et al., 2010). Despite well documented differences in specificity, emotional valence, and contextual detail between these memory types, it is apparent that ABM retrieval relies heavily upon the integrity of semantic information, with the converse observation that semantic memory relies on contextual and episodic components also holding true (Gilboa, 2004; Burianova et al., 2010). Thus, evidence from the study of neurodegenerative conditions serves to reinforce the view that the retrieval of autobiographical memories invariably involves a "synergy between semantic memory and contextual information" (Greenberg and Verfaellie, 2010, p. 749).

IMAGINING THE FUTURE – FUTURE ORIENTED THOUGHT

The arena of future oriented thought has undergone a dramatic surge of research activity within the last few years, with growing evidence in favor of a link between remembering the past, imagining the future, and engaging in mental simulation processes (Addis et al., 2007; Hassabis and Maguire, 2007; Hassabis et al., 2007; Schacter et al., 2012). The capacity to imagine specific events in the future has been shown to rely on a number of important component processes including the retrieval of sensory-perceptual episodic details, specificity, fluency, and phenomenological elements such as introspective processes, and the apprehension of subjective time (D'Argembeau et al., 2010). Two prominent theories have been proposed regarding the process by which humans engage in imagining future events. The scene construction hypothesis contends that the capacity to mentally generate and maintain a complex scene within a coherent spatial context represents a critical process which underpins a wide range of constructive processes, such as remembering the past, imagining the future, as well as atemporal and hypothetical simulation (Hassabis and Maguire, 2007, 2009). In contrast, the constructive episodic simulation hypothesis (Schacter and Addis, 2007a,b) holds that the extraction of episodic details from past memories, and their flexible recombination, is fundamental to the successful generation of novel future scenarios. Notably, the discovery that the capacity to envisage future events relies on the same neural machinery as retrieval of autobiographical events from the past (Addis et al., 2007; Szpunar et al., 2007; reviewed by Verfaellie et al., 2012) has proved influential in the resulting conceptualization of future oriented thought. Demonstrations of comparable activity across past and future conditions in the medial temporal lobes, anteromedial prefrontal cortices, posterior cingulate and retrosplenial cortex, lateral parietal and temporal areas has led to the hypothesis that a common "core" network underlies these capacities (Schacter et al., 2007, 2012; see **Figure 1**). In turn, the largely overlapping neurobiological substrates of past and future modes of thinking have led to the proposition that the capacity to mentally project oneself forward in subjective time is intimately linked to the ability to remember the past (Addis et al., 2007). Unsurprisingly, a sizeable proportion of studies have focused on the episodic component of future oriented thought, with the effects evident even down to the nomenclature of this construct ("episodic future thinking," Atance and O'Neill, 2001; Klein, 2013) although an episodic-semantic neutral conceptualization has recently been proposed (Stocker, 2012). Under the constructive episodic simulation hypothesis, a fundamental feature of the episodic memory system is its inherent constructive flexibility, which permits the creation of novel events not previously experienced (Schacter and Addis, 2007a,b). Damage to the episodic memory system, therefore, is expected to preclude the ability to mentally simulate future events.

PARALLEL DEFICITS ACROSS PAST AND FUTURE CONTEXTS IN ALZHEIMER'S DISEASE

The detection of equivalent deficits across past and future conditions in a range of clinical conditions, including AD (Addis et al., 2009), Mild Cognitive Impairment (Gamboz et al., 2010), schizophrenia (D'Argembeau et al., 2008), and depression (Williams et al., 1996) has strengthened the putative relationship between

autobiographical retrieval of the past and simulation of future events. In the study by Addis et al. (2009), patients with AD were found to exhibit marked difficulties in envisaging future events. Importantly these future thinking deficits correlated strongly with retrieval of past events. A recent study investigated the neural correlates of future thinking dysfunction in AD using voxel-based morphometry of structural MRI scans, and corroborated the close correspondence between episodic memory deficits and a compromised capacity for future thinking (Irish et al., 2012a). Crucially, parallel deficits across past and future contexts in AD were associated with disruption to key nodes of the core ABM network, notably the posterior cingulate cortex and the frontal poles. It seems likely that episodic memory dysfunction largely underpins the gross deficits exhibited by AD patients when they are attempting to envision their personal future. Accordingly, AD patients may rely on accessible abstracted semantic representations during future simulation, resulting in gist-based and overgeneral constructions. One area that remains underexplored to date concerns the potential role of scene construction processes as a contributory factor in future thinking dysfunction in AD. Irish et al. (2012a) documented that atrophy in the posterior cingulate cortex, and posterior parahippocampal gyrus correlated significantly with future thinking dysfunction in AD, regions which have been strongly implicated in the construction of spatially integrated scenes (Hassabis et al., 2007). Given the neural regions implicated in future thinking deficits in AD, it is therefore reasonable to assume that scene construction abilities will also be compromised in these patients. Thus, it remains unclear whether the prominent future thinking deficits observed in AD correspond to an impaired capacity for past retrieval, or difficulties with the construction of spatially coherent scenes, or perhaps, more likely, a confluence of multiple deficits arising from widespread neuronal damage to the core network.

THE ARRIVAL OF SEMANTIC MEMORY TO THE FUTURE THINKING LITERATURE

Greenberg and Verfaellie's (2010, p. 750) observation that "semantic memories are the basic material from which complex and detailed episodic memories are constructed" seems remarkably fitting when considered in relation to future oriented thinking. Research within the field of future thinking, however, has tended to eschew the possible contribution of semantic memory in favor of focusing on how future thinking may relate to the integrity of the episodic memory system (Klein, 2013). An early study of mental time travel in patient D.B. (Klein et al., 2002) served to reinforce the classic distinction between dissociable systems mediating episodic and semantic past and future thinking. Patient D.B. displayed profound deficits in his recollection of personal events from his past (episodic memory), which, in turn, impinged on his ability to project himself into the future. By contrast, D.B.'s semantic memory was largely preserved, enabling him to remember and to simulate events within the public, non-personal (semantic) domain (Klein et al., 2002). These findings served to reinforce previous views on the dissociation between episodic and semantic memory systems, and pointed toward distinct temporal divisions between what Klein (2013) termed "lived time" for the re-experiencing of the personal past, versus a "known time" in which semantic knowledge is drawn upon to enable temporal projection to the impersonal past.

Up until recently, the traditional heuristic of treating episodic and semantic memory as dissociable systems persisted into the future thinking domain. Klein (2013, p. 66) notes that as the relationship between episodic memory and future orientated thought has strengthened, researchers "simply may have overlooked the possibility that different types of memory contribute to future oriented temporal experience." A number of anomalies emerged within the literature, whereby experimental findings could not be adequately subsumed under models that exclusively emphasized the role of episodic memory in future oriented thought. In an fMRI study of past and future oriented thinking in personal (episodic) and non-personal (semantic) domains, Abraham et al. (2008b) reported functional dissociations between past and future, and between personal versus non-personal conditions. Importantly, significant engagement of semantic regions, including the inferior temporal gyrus and temporal poles, was observed irrespective of temporality or self-referential condition. Most notable is the observation that patients with developmental amnesia, as a consequence of hippocampal damage, displayed in some instances a preserved capacity to construct future experiences (Maguire et al., 2010b; Hurley et al., 2011; Mullally et al., 2012). Explanations for this relative preservation of future thinking abilities included the possibility that such patients could harness residual hippocampal function to support future projection (Maguire et al., 2010b; Mullally et al., 2012), but also the suggestion that semantic knowledge is an important facet of such imagined scenarios (Cooper et al., 2011; Hurley et al., 2011).

A COMPROMISED CAPACITY FOR FUTURE THINKING IN SEMANTIC DEMENTIA

While previous studies pointed to the possible contribution of semantic memory for future oriented thought, the first empirical demonstration that both episodic and semantic memory systems need to be functional to facilitate future thinking has emerged only recently. Duval et al. (2012) investigated the ability of patients with SD to form self-representations across past, present, and future contexts. While patients with SD demonstrated an intact capacity to retrieve recent self-representations, a striking impairment was observed when these patients envisaged their possible future selves. This deficit manifested in a marked inability to construct future self-images or to provide relevant contextual details to support their conception of their future selves (Duval et al., 2012). The authors concluded that personal semantic information therefore makes an important contribution to future oriented self-projection.

The asymmetric impairment of future with respect to past oriented thought was corroborated by another study that explicated the neural underpinnings of episodic and semantic future thinking impairments in SD (Irish et al., 2012a). Participants were required to remember three spatiotemporally specific events from the preceding year, and were asked to envisage three novel future events that might occur within the next year. Using the AI scoring procedure, a marked incapacity for future simulation was found in SD, despite their relatively intact retrieval of recent episodic events. Voxel-based morphometry analyses revealed that these

striking future thinking deficits in SD robustly correlated with brain regions known to underpin semantic representations (Visser et al., 2010), namely the left anterior inferior temporal gyrus and the bilateral temporal poles (Irish et al., 2012a; see **Figure 3**). Crucially, these results suggest that the retrieval of past episodes alone is not sufficient for the successful simulation of future events (see also Hassabis and Maguire, 2007; Andelman et al., 2010) and that regions beyond the classic episodic memory system are implicated in complex cognitive endeavors of this kind (Binder et al., 2009; Irish et al., 2012c).

DIFFERENTIAL DISRUPTION OF CONTEXTUAL DETAILS DURING FUTURE THINKING IN SD

The specific vulnerability of future simulation in SD is noteworthy as it speaks to the complexity of this cognitive construct. Further, the findings from the SD literature challenge the prevailing view of future simulation, which to date has focused primarily on the role of the medial temporal lobe and episodic memory (Schacter and Addis, 2007a,b; Race et al., 2011). Given the relative preservation of recent episodic memory in SD, and the profound deficits observed when these patients attempt to envisage their futures, it has been suggested that certain types of details may be differentially disrupted as the patient attempts to move from past to future contexts (Irish et al., 2012a). While much of the research impetus to date has focused on the relationship between episodic memory and future simulation, the extent to which the content of imagined future scenarios reflects elements of episodic memories remains unclear (Szpunar, 2010a). A recent analysis of the types of contextual details reported during future simulation in SD has offered important insights into the component processes underlying the capacity for future oriented thought. Irish et al. (2012b) dissected the types of contextual details embedded within past and future narratives using the AI scoring protocol, and investigated the profiles of contextual details for internal (episodic) and external (non-episodic) subscales. The fine-grained analysis of contextual details in SD has previously pointed to the disruption of recent spatiotemporal and emotional internal details during autobiographical retrieval (Irish et al., 2011a), whereas external details have been shown to be uniquely elevated in this group (McKinnon et al., 2008). Importantly, Irish et al. (2012b) reported that SD patients' generation of internal event details (i.e., those details conveying the crux of the episode) showed an asymmetric profile (past > future effect), whereby recent past retrieval was within Control levels yet such details were profoundly impaired exclusively in the future condition. In contrast, SD patients demonstrated a future > past effect for external event details, that is, those details which are believed to reflect non-episodic, or semantic, information (Irish et al., 2012b).

The asymmetric decline of internal, and concurrent elevation of external, details during future simulation in SD mirrors that previously demonstrated in healthy aging for retrieval of past autobiographical memories (Levine et al., 2002), and simulation of future events (Gaesser et al., 2011) albeit to an exaggerated degree. Of significance here, however, is the observation that while internal event details can be readily extracted from the past in SD, and remain available during the process of simulation, the construction of a future event ultimately fails. This finding underscores previous observations that thinking about the future necessarily draws upon contributions from both episodic and semantic memory (D'Argembeau and Mathy, 2011; Klein, 2013). In parallel with the failure to utilize readily available episodic details from the past, is the observation that SD patients produce a preponderance of off-target information not directly relevant to the event being simulated. At first glance, the over-production of non-episodic content in a cohort typified by marked semantic deficits seems counterintuitive, however, Irish et al. (2012b) note that such external details, in fact, represent off-target retrieval from unrelated past episodes. Thus the information provided by the SD patients is largely episodic, albeit unrelated to the event being simulated.

These recent findings are important as they resonate with a review article which questioned whether the strict reliance on the

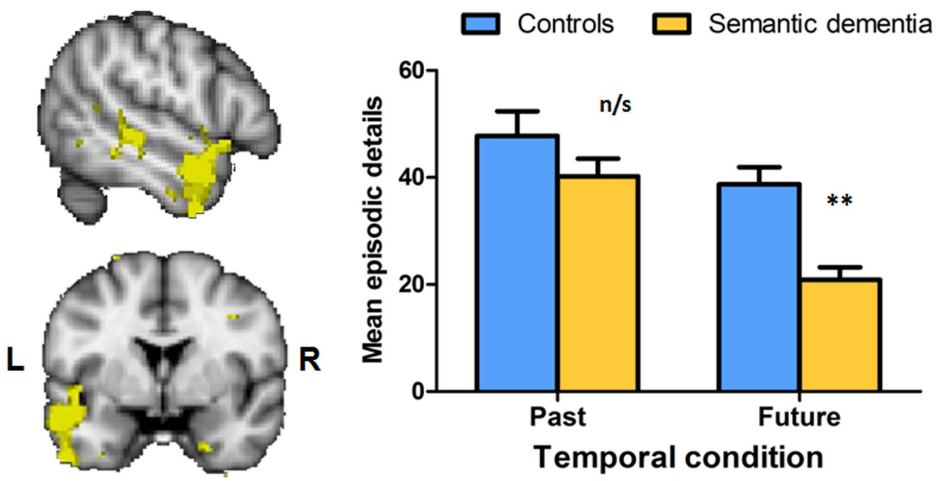


FIGURE 3 | Deficits in future thinking in semantic dementia are exclusively associated with gray matter intensity decrease in the left anterior temporal lobe, as revealed by voxel-based morphometry analyses. Clusters are significant at $P < 0.001$ and overlaid on the Montreal Neurological Institute standard brain. Error bars represent standard error of the mean. $^{**}P < 0.0001$; n/s, not significant. Figure adapted from Irish et al. (2012a).

contents of episodic memory represents the most efficient route to construct future scenarios (Szpunar, 2010a). By this view, Szpunar (2010a) reasons that the contribution of episodic and semantic elements during future simulation will invariably depend upon the accessibility of information that is relevant to the event of interest. Crucially, the content of any future simulation will reflect the information that is most readily accessible (Kahneman and Tversky, 1982; Szpunar, 2010a,b). Healthy individuals are likely to draw upon abstracted representations and such representations should, in general, be more accessible than specific one-off episodic representations (Szpunar, 2010a). In contrast, certain scenarios may exist in which episodic representations of specific events may represent the most efficient mode for future thinking. If we consider the findings from the SD patients in the Irish et al. (2012a,b) series, it becomes evident that the information most accessible to these patients is that of unique recent episodic occurrences and more general repeated events or "repisodes" in the absence of general conceptual semantic knowledge.

THE SEMANTIC SCAFFOLDING HYPOTHESIS

If episodic details represent the most accessible and efficient means for SD patients to construct a future scenario, why then are these details so vulnerable during future simulation? In line with current views emphasizing the importance of episodic and semantic contributions during future thinking, the findings from SD studies offer compelling evidence that the disintegration of the conceptual knowledge base adversely affects the ability to construct events in the future (Irish et al., 2012a). In this light, the recently proposed semantic scaffolding hypothesis is particularly pertinent, whereby semantic knowledge appears to provide a framework or scaffolding which facilitates past retrieval and future thinking (Greenberg and Verfaellie, 2010; Irish et al., 2012a). This semantic scaffolding hypothesis is relevant to the finding that a loss of semantic knowledge precludes the ability to simulate novel future events. In SD, the successful extraction of sensory-perceptual details from recent events occurs in the absence of the necessary conceptual framework to impart overall structure to the scenario (Irish et al., 2012b). If extraction of episodic details from the past represents the building blocks of future simulations, any attempt to construct a coherent scenario without the necessary scaffold or framework, results in the provision of a series of unrelated mini-events. Essentially, the episodic details cannot be integrated within the appropriate schema or abstracted representation from semantic memory. One further issue to disentangle, in this regard, is at which point in the simulation process semantic memory becomes pivotal? SD patients may not possess the relevant abstracted semantic representations to facilitate the construction of future events; however, a second possibility is that the loss of conceptual knowledge in SD also adversely impacts on the integrative mechanism necessary to bind episodic details into a coherent simulation. The final product of a successful future simulation likely comprises elements of various episodic and semantic details that are flexibly recombined to create an integrated and coherent representation of a specific future event (Szpunar, 2010a; Addis et al., 2011). It remains unknown, however, whether the amodal loss of semantic knowledge in SD precludes the recombination of episodic details from past retrieval into a coherent novel scenario, although this proposal represents an intriguing and plausible explanation for the elevation of unrelated event details in this group (Irish et al., 2012b). Further work is necessary to elucidate the precise mechanisms of detail recombination and, specifically, whether the reconfiguring of past details entails some form of semantic associative processing. It is possible that recombination may reflect a two-step process, in which firstly semantic associations between disparate details are made, drawing on abstracted representations that are accessible contingent on the specific task requirements, following which a process of integrative binding is required to flexibly recombine these details together into a coherent spatiotemporal framework. Determining the precise constituent elements of recombination within semantic frameworks represents an important line of enquiry for future research.

SEMANTIC KNOWLEDGE AND NOVELTY OF FUTURE SIMULATIONS

Semantic memory may be particularly important for the simulation of novel future events, in which no prior experience can be drawn upon from episodic memory. By its nature, semantic memory can be generalized to many different contexts (Mion et al., 2010), thus providing undifferentiated conceptual information that can be drawn upon to facilitate novel event construction (Binder and Desai, 2011; Irish et al., 2012a). The novelty of the simulated event becomes of paramount importance when we consider the profound difficulties experienced by patients with SD in envisioning events that have not occurred previously. Irish et al. (2012a) found that 80% of future events described by SD patients represented events that had been previously experienced in their entirety. Simply put, the SD patients demonstrated a marked propensity to sample past episodes and to recapitulate these events into the future condition, despite explicit task instructions requiring them to generate novel events not previously experienced. The severe semantic impairment in SD, therefore, disrupts the capacity for novel event generation, manifesting in scenarios that have been recast from intact past memories (Irish et al., 2012b). Recasting of the past is an intriguing phenomenon in SD, and suggests that the construction of novel events critically relies on the harnessing and deployment of semantic knowledge. By this argument, events which occur within familiar and repeated spatiotemporal contexts may be more readily accessible in SD, as the patients can successfully retrieve prior instances within such familiar contexts (Graham et al., 1999; Irish et al., 2011a). It may be that the envisaging of novel scenarios, for which one has little to no prior episodic experience, heavily taxes the semantic memory system, requiring the individual to draw on general world knowledge to guide them in their constructive endeavor. In SD, however, the progressive deterioration of the semantic memory system renders such conceptual knowledge inaccessible, causing the patient to overly rely on previously encountered scenarios, and ultimately resulting in the recapitulation of past events into the future condition.

It has recently been suggested that the creation of a suitable "situation model" represents a crucial process to facilitate the retrieval of past, and simulation of future, events (Ranganath and Ritchey, 2012). The successful formation of a situation model is, in turn, posited to depend on the integrity of a posterior medial cortical

system centered on the posterior parahippocampal cortex and retrosplenial cortex (Ranganath and Ritchey, 2012). This view corroborates previous fMRI studies of healthy individuals engaging in future simulation, in which the importance of posterior regions including the posterior cingulate cortex and parahippocampal cortex in the activation of well-known contextual settings has been emphasized (Szpunar et al., 2009). Notably, posterior brain regions remain relatively preserved until later in SD. These posterior regions offer a potential neuroanatomical signature for the harnessing of familiar contexts effect that is reliably demonstrated in future thinking studies in SD. Accordingly, SD patients draw upon the accessible situation model but cannot integrate or update this model to create a novel scenario, and inevitably recapitulate overgeneral or previously experienced events during future simulation. Further exploration of this recasting of familiar contexts effect in SD is clearly warranted, in particular how this phenomenon is related to the observation of an intact capacity to generate "repisodes" (Neisser, 1981) during ABM retrieval (Greenberg and Verfaellie, 2010). Likewise, an obvious outstanding area of research relates to whether the amodal loss of semantic knowledge in SD precludes the construction of spatially coherent scenes, in line with the scene construction theory advanced by Hassabis and Maguire (2007) and Hassabis et al. (2007). Unraveling the contribution of semantic memory to scene construction processes will be essential in clarifying the precise role of conceptual knowledge in memory and imagination.

CONCLUDING REMARKS

We conclude this review at an exciting juncture in episodic memory research. What has become evident is the incontrovertible extent to which episodic and semantic memory interact during complex forms of past and future oriented thinking, and the limitations of couching such endeavors within the traditional taxonomy of episodic and semantic memory as dissociable systems. The studying of complex cognitive processes in neurodegenerative conditions has proved critical for explicating how episodic and semantic elements may work in concert during autobiographical retrieval and future simulation, yet much remains to be elucidated. We suggest that concerted efforts are warranted to disentangle and elucidate the precise contributions of each memory system to constructive recollective and simulative endeavors, which in turn will illuminate our understanding of the episodic memory system of the brain.

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REFERENCES

Abraham, A., von Cramon, D. Y., and Schubotz, R. I. (2008a). Meeting George Bush versus meeting Cinderella: the neural response when telling apart what is real from what is fictional in the context of our reality. *J. Cogn. Neurosci.* 20, 965–976.

Abraham, A., Schubotz, R. I., and von Cramon, D. Y. (2008b). Thinking about the future versus the past in personal and non-personal contexts. *Brain Res.* 1233, 106–119.

Addis, D. R., Cheng, T., Roberts, R. P., and Schacter, D. L. (2011). Hippocampal contributions to the episodic simulation of specific and general future events. *Hippocampus* 21, 1045–1052.

Addis, D. R., Moscovitch, M., Crawley, A. P., and McAndrews, M. P. (2004). Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus* 14, 752–762.

Addis, D. R., Sacchetti, D. C., Ally, B. A., Budson, A. E., and Schacter, D. L. (2009). Episodic simulation of future events is impaired in mild Alzheimer's disease. *Neuropsychologia* 47, 2660–2671.

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377.

Adlam, A., Patterson, K., and Hodges, J. R. (2009). "I remember it as if it were yesterday": memory for recent events in patients with semantic dementia. *Neuropsychologia* 47, 1344–1351.

Andelman, F., Hoofien, D., Goldberg, I., Aizenstein, O., and Neufeld, M. (2010). Bilateral hippocampal lesion and a selective impairment of the ability for mental time travel. *Neurocase* 16, 426–435.

Atance, C. M., and O'Neill, D. K. (2001). Episodic future thinking. *Trends Cogn. Sci. (Regul. Ed.)* 5, 533–539.

Barense, M. D., Rogers, T. T., Bussey, T. J., Saksida, L. M., and Graham, K. S. (2010). Influence of conceptual knowledge on visual object discrimination: insights from semantic dementia and MTL amnesia. *Cereb. Cortex* 20, 2568–2582.

Barnabe, A., Whitehead, V., Pilon, R., Arsenault-Lapierre, G., and Chertkow, H. (2012). Autobiographical memory in mild cognitive impairment and Alzheimer's disease: a comparison between the Levine and Kopelman interview methodologies. *Hippocampus* 22, 1809–1825.

Barsalou, L. W. (1988). "The content and organisation of autobiographical memories," in *Remembering Reconsidered: Ecological and Traditional Approaches to the Study of Memory*, eds U. Neisser, and E. Winograd (New York: Cambridge University Press), 193–243.

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci. (Regul. Ed.)* 15, 527–536.

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–2796.

Bozeat, S., Gregory, C. A., Ralph, M. A., and Hodges, J. R. (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J. Neurol. Neurosurg. Psychiatr.* 69, 178–186.

Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–249.

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38.

Burianova, H., McIntosh, A. R., and Grady, C. L. (2010). A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *Neuroimage* 49, 865–874.

Butters, N., Granholm, E., Salmon, D. P., Grant, I., and Wolfe, J. (1987). Episodic and semantic memory: a comparison of amnesic and demented patients. *J. Clin. Exp. Neuropsychol.* 9, 479–497.

Cabeza, R., and St. Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends Cogn. Sci.* 11, 219–227.

Cermak, L. (1984). *The Episodic-Semantic Distinction in Amnesia.* New York: Guilford Press.

Chan, D., Fox, N., Scahill, R., Crum, W., Whitwell, J., Leschziner, G., et al. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann. Neurol.* 49, 433–442.

Conway, M. A. (2001). Sensory–perceptual episodic memory and its context: autobiographical memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1375–1384.

Conway, M. A., Singer, J. A., and Tagini, A. (2004). The self and autobiographical memory: correspondence and coherence. *Soc. Cogn.* 22, 491–529.

Cooper, J. M., Vargha-Khadem, F., Gadian, D. G., and Maguire, E. A. (2011). The effect of hippocampal damage in children on recalling the past and imagining new experiences. *Neuropsychologia* 49, 1843–1850.

Crutch, S. J., and Warrington, E. K. (2002). Preserved calculation skills in a case of semantic dementia. *Cortex* 38, 389–399.

D'Argembeau, A., and Mathy, A. (2011). Tracking the construction of episodic future thoughts. *J. Exp. Psychol. Gen.* 140, 258–271.

D'Argembeau, A., Ortoleva, C., Jumentier, S., and Van der Linden, M. (2010). Component processes underlying future thinking. *Mem. Cognit.* 38, 809–819.

D'Argembeau, A., Raffard, S., and Van der Linden, M. (2008). Remembering the past and imagining the future in schizophrenia. *J. Abnorm. Psychol.* 117, 247.

de Toledo-Morrell, L., Dickerson, B., Sullivan, M. P., Spanovic, C., Wilson, R., and Bennett, D. A. (2000). Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus* 10, 136–142.

Duval, C., Desgranges, B., De La Sayette, V., Belliard, S., Eustache, F., and Piolino, P. (2012). What happens to personal identity when semantic knowledge degrades? A study of the self and autobiographical memory in semantic dementia. *Neuropsychologia* 50, 254–265.

Eustache, F., Piolino, P., Giffard, B., Viader, F., De La Sayette, V., Baron, J. C., et al. (2004). "In the course of time": a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer's disease. *Brain* 127, 1549–1560.

Ewers, M., Sperling, R. A., Klunk, W. E., Weiner, M. W., and Hampel, H. (2011). Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends Neurosci.* 34, 430–442.

Gaesser, B., Sacchetti, D. C., Addis, D. R., and Schacter, D. L. (2011). Characterizing age-related changes in remembering the past and imagining the future. *Psychol. Aging* 26, 80–84.

Gallo, D. A., Shahid, K. R., Olson, M. A., Solomon, T. M., Schacter, D. L., and Budson, A. E. (2006). Overdependence on degraded gist memory in Alzheimer's disease. *Neuropsychology* 20, 625–632.

Galton, C., Patterson, K., Graham, K., Lambon-Ralph, M., Williams, G., Antoun, N., et al. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 57, 216–225.

Gamboz, N., De Vito, S., Brandimonte, M. A., Pappalardo, S., Galeone, F., Iavarone, A., et al. (2010). Episodic future thinking in amnesic mild cognitive impairment. *Neuropsychologia* 48, 2091–2097.

Gilboa, A. (2004). Autobiographical and episodic memory – one and the same? *Neuropsychologia* 42, 1336–1349.

Graham, K. S., and Hodges, J. R. (1997). Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: evidence from the study of semantic dementia and Alzheimer's disease. *Neuropsychology* 11, 77–89.

Graham, K. S., Patterson, K., and Hodges, J. R. (1999). Episodic memory: new insights from the study of semantic dementia. *Curr. Opin. Neurobiol.* 9, 245–250.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., and Hodges, J. R. (2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia* 38, 313–324.

Greenberg, D. L., Ogar, J. M., Viskontas, I. V., Gorno Tempini, M. L., Miller, B., and Knowlton, B. J. (2011). Multimodal cuing of autobiographical memory in semantic dementia. *Neuropsychology* 25, 98–104.

Greenberg, D. L., and Verfaellie, M. (2010). Interdependence of episodic and semantic memory: evidence from neuropsychology. *J. Int. Neuropsychol. Soc.* 16, 748–753.

Greene, J., Hodges, J. R., and Baddeley, A. (1995). Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia* 33, 1647–1670.

Hassabis, D., Kumaran, D., and Maguire, E. A. (2007). Using imagination to understand the neural basis of episodic memory. *J. Neurosci.* 27, 14365–14374.

Hassabis, D., and Maguire, E. A. (2007). Deconstructing episodic memory with construction. *Trends Cogn. Sci. (Regul. Ed.)* 11, 299–306.

Hassabis, D., and Maguire, E. A. (2009). The construction system of the brain. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 364, 1263–1271.

Hodges, J. R., and Graham, K. S. (2001). Episodic memory: insights from semantic dementia. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1423–1434.

Hodges, J. R., and Patterson, K. (2007). Semantic dementia: a unique clinicopathological syndrome. *Lancet Neurol.* 6, 1004–1014.

Hou, C., Miller, B., and Kramer, J. (2005). Patterns of autobiographical memory loss in dementia. *Int. J. Geriatr. Psychiatry* 20, 809–815.

Hurley, N. C., Maguire, E. A., and Vargha-Khadem, F. (2011). Patient HC with developmental amnesia can construct future scenarios. *Neuropsychologia* 49, 3620–3628.

Hussey, E. P., Smolinsky, J. G., Piryatinsky, I., Budson, A. E., and Ally, B. A. (2012). Using mental imagery to improve memory in patients with Alzheimer's disease. *Alzheimer Dis. Assoc. Disord.* 26, 124–134.

Irish, M., Addis, D. R., Hodges, J. R., and Piguet, O. (2012a). Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain* 135, 2178–2191.

Irish, M., Addis, D. R., Hodges, J. R., and Piguet, O. (2012b). Exploring the content and quality of episodic future simulations in semantic dementia. *Neuropsychologia* 50, 3488–3495.

Irish, M., Piguet, O., and Hodges, J. R. (2012c). Self-projection and the default network in frontotemporal dementia. *Nat. Rev. Neurol.* 8, 152–161.

Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., et al. (2006). Investigating the enhancing effect of music on autobiographical memory in mild Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 22, 108–120.

Irish, M., Hornberger, M., Lah, S., Miller, L., Pengas, G., Nestor, P. J., et al. (2011a). Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia* 49, 2694–2702.

Irish, M., Lawlor, B. A., O'Mara, S. M., and Coen, R. F. (2011b). Impaired capacity for autonoetic reliving during autobiographical event recall in mild Alzheimer's disease. *Cortex* 47, 236–249.

Irish, M., Lawlor, B. A., O'Mara, S. M., and Coen, R. F. (2008). Assessment of behavioural markers of autonoetic consciousness during episodic autobiographical memory retrieval: a preliminary analysis. *Behav. Neurol.* 19, 3–6.

Kahneman, D., and Tversky, A. (1982). "The simulation heuristic," in *Judgment Under Uncertainty*, eds D. Kahneman, P. Slovic, and A. Tversky (Cambridge: Cambridge University Press), 201–208.

Kihlstrom, J. F. (1984). A fact is a fact is a fact [commentary]. *Behav. Brain Sci.* 7, 243–244.

Klein, S. B. (2013). The complex act of projecting oneself into the future. *Wiley Interdiscip. Rev. Cogn. Sci.* 4, 63–79.

Klein, S. B., Loftus, J., and Kihlstrom, J. F. (2002). Memory and temporal experience: the effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. *Soc. Cogn.* 20, 353–379.

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.* 11, 724–744.

Kosslyn, S. M., Ganis, G., and Thompson, W. L. (2001). Neural foundations of imagery. *Nat. Rev. Neurosci.* 2, 635–642.

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol. Aging* 17, 677–689.

Leyhe, T., Muller, S., Milian, M., Eschweiler, G. W., and Saur, R. (2009). Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia* 47, 2464–2469.

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1441–1451.

Maguire, E. A., Kumaran, D., Hassabis, D., and Kopelman, M. D. (2010a). Autobiographical memory in semantic dementia: a longitudinal fMRI study. *Neuropsychologia* 48, 123–136.

Maguire, E. A., Vargha-Khadem, F., and Hassabis, D. (2010b). Imagining fictitious and future experiences: evidence from developmental amnesia. *Neuropsychologia* 48, 3187–3192.

Matuszewski, V., Piolino, P., Belliard, S., De La Sayette, V., Laisney, M., Lalevée, C., et al. (2009). Patterns of autobiographical memory impairment according to disease severity in semantic dementia. *Cortex* 45, 456–472.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R. Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269.

McKinnon, M., Black, S., Miller, B., Moscovitch, M., and Levine, B. (2006). Autobiographical memory in semantic dementia: implications for theories of limbic-neocortical interaction in remote memory. *Neuropsychologia* 44, 2421–2429.

McKinnon, M., Nica, E., Sengdy, P., Kovacevic, N., Moscovitch, M., Freedman, M., et al. (2008). Autobiographical memory and patterns of brain atrophy in fronto-temporal lobar degeneration. *J. Cogn. Neurosci.* 20, 1839–1853.

Mesulam, M. M., Wieneke, C., Hurley, R., Rademaker, A., Thompson, C. K., Weintraub, S., et al. (2013). Words and objects at the tip of the left temporal lobe in primary progressive aphasia. *Brain* 136, 601–618.

Mion, M., Patterson, K., Acosta-Cabronero, J., Pengas, G., Izquierdo-Garcia, D., Hong, Y. T., et al. (2010). What the left and right anterior fusiform gyri tell us about semantic memory. *Brain* 133, 3256–3268.

Moss, H. E., Kopelman, M. D., Cappelletti, M., Davies Pde, M., and Jaldow, E. (2003). Lost for words or loss of memories? Autobiographical memory in semantic dementia. *Cogn. Neuropsychol.* 20, 703–732.

Mullally, S. L., Hassabis, D., and Maguire, E. A. (2012). Scene construction in amnesia: an FMRI study. *J. Neurosci.* 32, 5646–5653.

Neisser, U. (1981). John Dean's memory: a case study. *Cognition* 9, 1–22.

Nestor, P. J., Graham, K. S., Bozeat, S., Simons, J. S., and Hodges, J. R. (2002). Memory consolidation and the hippocampus: further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. *Neuropsychologia* 40, 633–654.

Patterson, K., Nestor, P., and Rogers, T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat. Rev. Neurosci.* 8, 976–987.

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De La Sayette, V., et al. (2003). Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. *Brain* 126, 2203–2219.

Race, E., Keane, M. M., and Verfaellie, M. (2011). Medial temporal lobe damage causes deficits in episodic memory and episodic future thinking not attributable to deficits in narrative construction. *J. Neurosci.* 31, 10262–10269.

Ranganath, C., and Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nat. Rev. Neurosci.* 13, 713–726.

Reder, L. M., Park, H., and Kieffaber, P. D. (2009). Memory systems do not divide on consciousness: reinterpreting memory in terms of activation and binding. *Psychol. Bull.* 135, 23–49.

Ribot, T. (1881). *Les maladies de la mémoire.* Paris: Germer Baillière.

Rogers, T. T., Lambon Ralph, M. A., Garrard, P., Bozeat, S., McClelland, J. L., Hodges, J. R., et al. (2004). Structure and deterioration of semantic memory: a neuropsychological and computational investigation. *Psychol. Rev.* 111, 205–235.

Rosenbaum, R. S., Winocur, G., and Moscovitch, M. (2001). New views on old memories: re-evaluating the role of the hippocampal complex. *Behav. Brain Res.* 127, 183–197.

Schacter, D. L., and Addis, D. R. (2007a). The cognitive neuroscience of constructive memory: remembering the past and imagining the future. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 773–786.

Schacter, D. L., and Addis, D. R. (2007b). On the constructive episodic simulation of past and future events. *Behav. Brain Sci.* 30, 331–332.

Schacter, D. L., Addis, D. R., and Buckner, R. L. (2007). Remembering the past to imagine the future: the prospective brain. *Nat. Rev. Neurosci.* 8, 657–661.

Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., and Szpunar, K. (2012). The future of memory: remembering, imagining, and the brain. *Neuron* 76, 677–694.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 280–292.

Spreng, R. N., Mar, R. A., and Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J. Cogn. Neurosci.* 21, 489–510.

Squire, L., and Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177.

Stocker, K. (2012). The time machine in our mind. *Cogn. Sci.* 36, 385–420.

Suddendorf, T., and Corballis, M. (2007). The evolution of foresight: what is mental time travel, and is it unique to humans? *Behav. Brain Sci.* 30, 299–313.

Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208.

Szpunar, K. (2010a). Episodic future thought. *Perspect. Psychol. Sci.* 5, 142.

Szpunar, K. (2010b). Evidence for an implicit influence of memory on future thinking. *Mem. Cognit.* 38, 531–540.

Szpunar, K., Chan, J. C., and McDermott, K. B. (2009). Contextual processing in episodic future thought. *Cereb. Cortex* 19, 1539–1548.

Szpunar, K., Watson, J., and McDermott, K. B. (2007). Neural substrates of envisioning the future. *Proc. Natl. Acad. Sci. U.S.A.* 104, 642–647.

Tulving, E. T. (1995). "Organization of memory: quo vadis?" in *The Cognitive Neurosciences,* ed. M. S. Gazzaniga (Cambridge, MA: MIT Press), 839–847.

Tulving, E. T. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25.

Tulving, E. T., and Szpunar, K. (2009). Episodic memory. *Scholarpedia* 4, 3332.

Van Hoeck, N., Ma, N., Ampe, L., Baetens, K., Vandekerckhove, M., and Van Overwalle, F. (in press). Counterfactual thinking: an fMRI study on changing the past for a better future. *Soc. Cogn. Affect. Neurosci.* doi:10.1093/scan/nss031

Vartanian, O. (2012). Dissociable neural systems for analogy and metaphor: implications for the neuroscience of creativity. *Br. J. Psychol.* 103, 302–316.

Verfaellie, M., Race, E., and Keane, M. M. (2012). Medial temporal lobe contributions to future thinking: evidence from neuroimaging and amnesia. *Psychol. Belg.* 52, 77–94.

Visser, M., Embleton, K. V., Jefferies, E., Parker, G. J., and Ralph, M. A. (2010). The inferior, anterior temporal lobes and semantic memory clarified: novel evidence from distortion-corrected fMRI. *Neuropsychologia* 48, 1689–1696.

Ween, J. E., Verfaellie, M., and Alexander, M. P. (1996). Verbal memory function in mild aphasia. *Neurology* 47, 795–801.

Westmacott, R., Leach, L., Freedman, M., and Moscovitch, M. (2001). Different patterns of autobiographical memory loss in semantic dementia and medial temporal lobe amnesia: a challenge to consolidation theory. *Neurocase* 7, 37–55.

Whitwell, J. L., Josephs, K. A., Rossor, M. N., Stevens, J. M., Revesz, T., Holton, J. L., et al. (2005). Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. *Arch. Neurol.* 62, 1402–1408.

Williams, J. M., Ellis, N. C., Tyers, C., Healy, H., Rose, G., and Macleod, A. K. (1996). The specificity of autobiographical memory and imageability of the future. *Mem. Cognit.* 24, 116–125.

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Making the case that episodic recollection is attributable to operations occurring at retrieval rather than to content stored in a dedicated subsystem of long-term memory

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Episodic memory often is conceptualized as a uniquely human system of long-term memory that makes available knowledge accompanied by the temporal and spatial context in which that knowledge was acquired. Retrieval from episodic memory entails a form of first–person subjectivity called autonoetic consciousness that provides a sense that a recollection was something that took place in the experiencer's personal past. In this paper I expand on this definition of episodic memory. Specifically, I suggest that (1) the core features assumed unique to episodic memory are shared by semantic memory, (2) episodic memory cannot be fully understood unless one appreciates that episodic recollection requires the coordinated function of a number of distinct, yet interacting, "enabling" systems. Although these systems—ownership, self, subjective temporality, and agency—are not traditionally viewed as memorial in nature, each is necessary for episodic recollection and jointly they may be sufficient, and (3) the type of subjective awareness provided by episodic recollection (autonoetic) is relational rather than intrinsic—i.e., it can be lost in certain patient populations, thus rendering episodic memory content indistinguishable from the content of semantic long-term memory.

Keywords: episodic memory, semantic memory, autonoetic awarness, amnesia, self, consciousness

What is episodic memory? As initially conceptualized, it is a system of long-term memory whose content provided its owner with a record of the temporal, spatial and self-referential features of the context in which the original learning transpired (e.g., Tulving, 1972, 1983). By contrast, semantic long-term memory lacked these features: Its offerings were experienced as knowledge devoid of the contextual elements in which it was acquired.

A clear implication of this distinction was the difference in subjective relations these systems of memory shared with the past. Episodic memory entailed awareness that a current recollection referred directly to, and thus was conceptualized as, an event that had transpired previously in one's life. By contrast, content from semantic memory was solely occurrent—it was present to awareness—as either thought or image—and though one could logically infer that the occurrent content must have been acquired at some time in one's past, the recollection of its acquisition was not part of its experienced presentation.

These temporal distinctions were fully appreciated by Tulving, and in 1985 he made them an explicit basis for distinguishing between episodic and semantic systems of memory (Tulving, 1985). Adopting terminology proposed originally by Husserl—"noesis" (i.e., the type of experience associated with thought and remembering; e.g., Husserl, 1964)—Tulving focused attention on the types temporal subjectivity accompanying the retrieval of episodic and semantic memory. Episodic memory was held to enable *autonoetic* awareness, while semantic memory enabled a type of awareness he termed *noetic* (e.g., Tulving, 1985, 1993, 2002; Wheeler et al., 1997; Szpunar and Tulving, 2011).

Autonoetic awareness was defined as "self-knowing": when autonoetically aware, the individual's phenomenology is characterized by "... a unique awareness of re-experiencing here and now something that happened before, at another time and in another place" (Tulving, 1993, p. 68). By contrast, noetic awareness occurs when one thinks objectively about something one knows. Individuals are said to be noetically aware when "they retrieve general information in the absence of a feeling of re-experiencing the past" (Szpunar, 2010, p. 144). Central to the proposed distinction: "Only 'autonoetic consciousness' is thought to bear a personally meaningful relation to time" (Szpunar and Tulving, 2011, p. 4).

Autnoetic and noetic awareness align naturally with episodic and semantic modes of remembering, respectively (Tulving, 1985, 1993, 2002; Wheeler et al., 1997). Only autonoetic experience is assumed capable of providing the subjective requirements for mental time travel (e.g., Suddendorf and Corballis, 1997, 2007; Wheeler et al., 1997; Tulving, 2002; but see Klein, 2013b). Accordingly, episodic memory is tied directly to temporally-rich autonoetic experience. By contrast, awareness of semantic knowledge (i.e., noetic) lacks a subjective sense that one is mentally traveling to back in time to the events and experiences in one's past that gave birth to that awareness.

Tulving's reformulation of episodic and semantic memory in terms of temporal subjectivity has been widely adopted by memory researchers and has shown to be a particularly fruitful way of generating testable hypotheses and theoretical models of the episodic and semantic division of long-term declarative

memory (e.g., Perner and Ruffman, 1994; Gardiner, 2001; Piolino et al., 2003; Wheeler, 2005; Markowitsch and Staniliou, 2011; for reviews, see Wheeler et al., 1997; Dere et al., 2008). A distinction based on subjective temporality also avoids a number of untidy findings that, over the years, have chipped away at the traditional classification of episodic and semantic memory in terms of the presence or absence of the criteria of time, space and self.

For instance, the assumption that episodic, rather than semantic, memory entails a self-referential component has given way to the well-recognized fact that knowledge in semantic memory also can be self-referential (for reviews, see Klein, 2010; Klein and Gangi, 2010; Klein and Lax, 2010; Renoult et al., in press). In addition, the content of semantic memory is capable of contributing to a knowledge-based representation that includes both spatial and temporal contextual information (e.g., "I know that John Lennon was born on October 9th, 1940 in Liverpool, UK, although I do not recollect the event in which that knowledge was acquired"; e.g., Tulving et al., 1988; Kopelman et al., 1989; Klein, 2001; for recent reviews see Klein, 2004; Klein and Gangi, 2010; Klein and Lax, 2010; Martinelli et al., 2012).

Thus, the core constituents of episodic memory as initially proposed (i.e., temporal, spatial, and self-referential) also can be on display in semantic memory experience. Indeed, there appears no principled reason why the content of these two systems should differ. This is demonstrated rather dramatically in a case presented by Stuss and Guzman (1988). An individual, who, as a result of illness, suffered profound retrograde episodic amnesia, nonetheless was able to successfully re-learn specific temporal and spatial details of his personal past. However, in accord with the autonoetic/noetic distinction, the patient experienced this content as semantic fact rather than as a re-living of his personal past (since he did not suffer comparable anterograde impairment, he could, of course, mentally travel back to the experienced events in which personal knowledge was relearned).

Thus, there is no logical argument or empirical evidence supporting the assertion that only episodic memory makes reference to the "where and when" of past personal experience. While the fact that two potentially separate systems share criteria is not a "death sentence" for a taxonomy, it highlights the severe difficulties faced by those who would adopt the "time, place, and self" criteria as *the* basis for classification.

In summary, the "time, space, and self" criterion for distinguishing between semantic and episodic memory is insufficient for the task for which it originally was designed. By contrast, the autonoetic/noetic criterion for classification does good work both in capturing a fundamental feature of our memory phenomenology and in serving as fertile theoretical and empirical grounds for exploring the complexities of the types of systems subsumed under the general designator "memory" (for reviews, see Wheeler, 2000; Markowitsch, 2003; Dere et al., 2008). In the next section I discuss issues involved in identifying an occurrent mental state as a memory.

MEMORY EXPERIENCE AND ITS CONNECTION TO THE PAST

The adoption of subjective temporality as a basis for distinguishing between forms of memory trades on the notion that the criteria for classification lie not in the *form* of content experienced, but in the *manner* in which that content is received by consciousness. In one sense, all memory-based content is experienced as occurrent—it is an act of mind happening *now*. As Reid puts it, "Every man can distinguish the thing remembered from the remembrance of it. We may remember anything we have seen, or heard, or known, of done, or suffered; but the remembrance of it is a particular act of the mind which now exists, and of which we are conscious" (Reid, 1813/1969, pp 324–325). It is the attachment of the "past" to present mental experience (be it imagistic or propositional) that marks the experience as one of memory rather than, say, imagination (Reid, by the way, denied the possibility of imagistic recollection, but that need not concern us at present).

The requirement that a current mental state evoke a sense of attachment to one's past to establish it as an act of memory (rather than, say, thought or imagination) long has been recognized. And, it has been a persistent thorn in the side of psychologists and philosophers grappling with the problem of placing a current mental state in a relation to the past. And, for the relation to do good work, it must be of the "right type."

So, what is the "right type" of relation between an occurrent mental state and the past? William James (1890), as so often is the case, puts the problem in sharp relief: "A farther condition is required before the present image can be held to stand for a *past original*. That condition is the fact that the imagined be *expressly referred to the past*, thought as *in the past* . . . But even that would not be memory. Memory requires more than mere dating of a fact in the past. It must be dated in *my* past. In other words, I must think that I directly experienced its occurrence. It must have . . . 'warmth and intimacy'. . . " (James, 1890, p. 650; emphasis in original).

Over the years (both prior to and following James' remarks) numerous criteria have been proposed to do the work of differentiating memory from a non-memorial mental content.[1] Hume famously proposed that the vivacity of a mental image is a basis on which we separate an image or thought from a memory, with memory being more lively and vivacious. He also proposed that the amount of "free play" we have with our mental states serves as a useful criterion—in contrast to imagining, for example, when

[1] Although James also is clear that much of what we now call semantic knowledge would not qualify as memory in his system—lacking, as it does, obvious reference to one's past (e.g., $2 + 2 = 4$; the sun is hot)—I believe that reference to the past is overly restrictive and not a necessary criterion for a mental experience or bodily action to meet the requirements for being a memory. A memory is an occurrent mental event that can be shown to have a causal connection to past experience. On this view, the expression of learning (whether via mental state or physical act) qualifies as memorial regardless of whether its current instantiation can be consciously traced to, or felt to derive from, a previously encountered event or experience, provided the proper causal connection(s) to a past experience can be demonstrated (via inference, objective evidence, or felt experience of past). For example, intelligently coordinated movements of the body which draw on the accumulated effect of knowable past events qualify as memorial despite absence of awareness that they are causally derived from previous experience (i.e., procedural memory). Of course, a little thought reveals an obvious circularity in any criterion of memory that draws on acquaintance (direct or indirect) with the past (i.e., memory) as the evidential basis for memory (e.g., Furlong, 1951). This perplexing conundrum would take us too far from the issues at hand and thus will not be dealt with here.

we remember we have less free play with mental content, since that content is bound by the past to represent things as they actually were (Hume, 1748/2004). Russell saw things differently, proposing that to be considered a memory a mental content must be accompanied by two feelings—pastness and familiarity (Russell, 1921).

Among modern psychological investigators, the work of Johnson and her colleagues represents the most systematic attempt to tackle this vexing problem (for review, see Johnson and Raye, 1981; Johnson et al., 1993). Their research eventuated in a set of criteria—e.g., the richness of the contextual and perceptual elements contained in a mental state. Although these criteria were proposed primarily to account for discrimination between memories for thoughts and memories for perceptions, they easily are adapted for classifying mental content as a memory as opposed to an act of thought or imagination.

Unfortunately, as theorists and philosophers have discovered, none of these criteria stand the test of logical analysis or introspection (for reviews, see Furlong, 1951; Casey, 1977; Warnock, 1987; Bernecker, 2010). For example, Russell's and Hume's assumption that the content of memory experience is "bound to the past" is partly undermined by demonstrations that memorial experience is, at least to a degree, reconstructive (e.g., Bartlett, 1932). And, we all have had experiences in which an imagination is vivid and a memory faint (e.g., Warnock, 1987). As Bernecker (2010) concluded, the problem with the memory-markers thus far proposed is that "they don't offer a reliable mark" (p. 22). Each is subject to logical argument and/or empirical demonstration that makes clear that none of the proposed criteria are either necessary or sufficient for marking a memory as such.

Considered in this light, the autonoetic/noetic criterion seems encouraging. While it may not serve as a definitive basis for distinguishing semantic memory from imagination—both are, by definition, noetic—it does provide a promising conceptual and phenomenological basis for identifying present mental content as part of one's past. It thus appears to be up to the task—that is, it provides the "right type" of relation—when the issue at hand is to determine whether an occurrent mental content is an episodic memory.

IS AUTONOETIC AWARENESS INTRINSIC TO EPISODIC RECOLLECTION?

Having argued in support of Tulving's contention that temporal subjectivity can serve as a useful basis by which to classify mental content as memorial, the issue now at hand is this—does subjective temporality provide sufficient license to conclude that current mental content represents an episodic, as opposed to a semantic, memory? As noted, content alone is not sufficient to make this judgment, since the constituents of both systems of memory *can* include temporal, spatial and self-referential elements. By contrast, the mode of subjective temporality accompanying an act of memory is assumed to differ dramatically between episodic recollection and semantic retrieval.

The content retrieved from semantic memory, on Tulving's account, can (at most) be *about* the past. Retrieval from semantic memory can be taken as either temporal (Klein et al., 2002b; for review, see Klein, 2013a) or atemporal (e.g., Klein et al., 2010). What determines its stance with respect to time is not the *quality* of the experience *per se*, but rather our ability to inferentially *refer* the experience to the past on the basis of the content present in (noetic) awareness. Thus, a causal analysis is required to place an occurrent semantic memory in a relation to the past.

On the other hand, episodic memory's connection to the past is not one of logical inference. Rather, it is pre-reflective, directly *given* (e.g., Zahavi, 2005). It is a sense (i.e., a feeling) that my current mental state stands for, and thus representative of, an experience in my personal past (e.g., James, 1890). The content of episodic recollection is given as being *of* the past; it is accompanied by a feeling of mental time travel—that is, re-visiting a personal experience. This feeling, or sense of attachment, to my past (which James called "warmth and intimacy" and Russell labeled "feelings of familiarity and pastness"), is part of the subjective *quality of* the mental event. As Nagel (1974) might say, the pastness of an episodic experience is part of "the feeling of what it is like" to have such an experience. And this feeling (or qualia) accompanying episodic recollection is made possible by episodic memory's association with autonoetic awareness.

The distinction between episodic and semantic memorial experience can thus be seen as one of differences in manner of acquaintance (e.g., Russell, 1912/1999). We are acquainted with semantic pastness indirectly via inference, whereas our acquaintance with episodic pastness is directly given as the feeling that we are re-living our past. If this distinction holds, then a phenomenological state is what differentiates our experience of these two forms of long-term memory.

So what exactly is the *connection* between autonoetic awareness and episodic memory? Two possibilities present themselves. Either (as commonly assumed, though seldom stated), autonoetic awareness is (1) *intrinsic* (i.e., necessary) to episodic memory—i.e., it is a part, or constituent, of "episodic" content, or (2) it has a *relational* (i.e., contingent) connection to memory content—i.e., while under normal circumstances it is observed to be coextensive with "episodic" content, this connection is one of contingency rather than necessity.

On the relational view, the neuro-cognitive mechanisms that make possible autonoetic awareness are functionally independent of the mechanisms that make available the content of long-term memory. What makes a memory experience episodic or semantic is not the nature of the content, or the hypothesized system in which content resides while in "storage," but rather an act of temporal (or atemporal) awareness that becomes associated with the content *once* it has been retrieved.

This is the view I champion in this paper. Although evidence in support is scarce, suggestive findings have been reported in a study by Piolino and colleagues (2003). Using the remember/know paradigm (e.g., Tulving, 1985), these investigators found that patients suffering Alzhiemer's Disease and Frontotemporal Dementia report significantly fewer "remember" responses than do controls. Based on this finding, they conclude that these two forms of dementia entail impairments specific to autonoetic awareness. However, whether this impairment occurs in storage or at retrieval is indeterminate. Moreover, as I discuss in section "Conclusions," the proposed relation between remember judgments and autonoeisis is more suggestive than theoretically

grounded. I present evidence that bears directly on the relation between autonoetic awareness and retrieval in section "Can Autonoetic Awareness be Separated from Episodic Content? The Case of Patient R. B."

In sum, the relational view implies that memory content is neither episodic nor semantic; rather retrieved content is classifiable as episodic or semantic by virtue of a concurrent act of autonoetic awareness, whose association (or lack thereof) is used to classify an occurrent mental state as episodic or semantic. Seen in this light, there are no systems of episodic and semantic memory *per se*. Rather, there is memory content that can, if a suitable candidate for temporal specification is present in consciousness (e.g., "where and when I learned that $2 + 2 = 4$," but not "I know that $2 + 2 = 4$") can be acted on by the autonoetic subsystem to confer a sense of temporal subjectivity on the content retrieved.[2]

EPISODIC MEMORY: A COMPONENTIAL APPROACH

Many contemporary treatments of episodic memory focus on the encoding, storage and retrieval of memory content (for discussion, see Klein, 2007). However, as Klein et al. (2004) have argued, theoretical and empirical considerations call into question the wisdom of such restrictive treatment of memory experience. Their work makes a strong case that episodic recollection entails a multiplicity of functionally independent, yet normally interacting, systems, only some of which bear an obvious a priori relation to memory taken as the encoding, storage and retrieval of content.

Specifically, Klein et al. (2004) proposed that to experience memory content as episodic requires, at a minimum, four capabilities. These include (1) a capacity for self-reflection; that is, the ability to reflect on my own mental states—to know about my own knowing, (2) a sense of personal agency; that is, the belief that I am the cause of my thoughts and actions, (3) a sense of personal ownership; that is, the feeling that my thoughts and acts belong to me, and (4) the ability to think about time as an unfolding of personal happenings centered about the self. Klein and colleagues conceptualized episodic recollection as a mental state resulting from the finely tuned interplay of these four psychological capacities that, working together, transform a retrieved content into an episodic experience. It follows that breakdowns in any of these components (self-reflection, self-agency, self-ownership, and personal temporality) should produce, in varying degrees, specific, highly circumscribed impairments in episodic recollection. A review of the available evidence showed that this does indeed occur (e.g., Klein, 2001; Klein et al., 2004), leading the authors to suggest that the subsystems identified may provide a set of individually necessary and jointly sufficient conditions for enabling memory content to be experienced as episodic recollection.

I will not review the specifics of the subsystems identified by Klein et al. (2004; for a related view, see Klein, 2011). Rather, in what follows I focus on one system with direct relevance to present concerns—the system that enables a feeling of ownership of one's mental states—and I discuss its implications for autonoetic awareness and its relation to episodic memory experience.

CAN AUTONOETIC AWARENESS BE SEPARATED FROM EPISODIC CONTENT? THE CASE OF PATIENT R. B.

As noted in Section "Is Autonoetic Awareness Intrinsic to Episodic Recollection?" if autonoetic awareness is functionally independent from memory content, then temporal subjectivity and memory content should be capable of being pried apart. The case of patient R. B. (reported below), has direct bearing on this issue.

The idea that ownership of one's mental states can come loose from the states, as experienced, is not a novel observation: A substantial literature (primarily clinical) speaks to the reality of this possibility. For example, in a largely speculative treatment, Jaynes (1976) argued that prior to acquiring the capacity to confer ownership on conscious thought our ancestors were unable to accurately localize the origination of "voices heard" in their heads. Less speculative evidence comes from cases of thought insertion in schizophrenics suffering delusional symptoms (e.g., Frith, 1992; Gallagher, 2000; Northoff, 2000; Bortolotti and Broome, 2009; for review, see Stephens and Graham, 2000). However, while these cases support the realizability, and thus conceivability, of a lack of personal ownership of one's mental states, schizophrenic patients *apparent* memories, even in early stages of the disorder, likely are delusions in some sense (e.g., Northoff, 2000; Klein and Nichols, 2012), and this renders such cases less than optimal as demonstrations that memory (as opposed to, say, delusion) and ownership can come apart.

Of particular importance, then, is the case of patient R. B. (the details are summarized herein. A fuller treatment can be found in Klein and Nichols, 2012). As a result of a serious accident, R. B. suffered, in addition to severe physical injuries, a number of cognitive impairments. These included difficulty in maintaining attention, mild aphasia, and retrograde and anterograde amnesia for events in close temporal proximity to the accident. His performance on tests of verbal fluency and short-term memory span fell below the scores provided by neurologically healthy age-matched controls.

While in the hospital, R. B. was placed on morphine (IV drip, followed by pills) and Oxycontin to alleviate the considerable pain he endured. As the intensity of his pain subsided, he weaned himself off medication. Importantly, at the time of testing R. B. was not on any pain medication. In addition, his long and short-term memory impairments, aphasia and fluency deficits had resolved.

Not all cognitive function, however, had returned to normal. Of direct bearing on the question at hand—the relation of autonoetic awareness to episodic memory—R. B. was able to remember particular incidents from his life accompanied by clear temporal, spatial and self-referential content. But he did not

[2]One limitation of the present account is that I have no proven criteria for specifying when autonoetic awareness will act on retrieved content other than the trivially obvious consideration of content relevance to temporal treatment [One speculative possibility—which I develop later in this paper—trades on Nadel and Moscovitch's (1997) Mutliple Trace Theory]. However, while the lack of a clear understanding of how and when autonoetic awareness makes contact with current mental content is an obvious weakness of my proposal, I do not think the absence of research on a previously un-proposed emendation to a well-established model argues, by itself, against the potential worth of my suggested revision. Rather, it highlights the novelty of the proposal and the need for conceptual and empirical work before the ideas expressed herein can transition from plausible to likely.

feel the content experienced belonged to him. In his words, they lacked "ownership"[3] (in the descriptive language of James, Russell, and Hume, his "memories" lacked feelings of warmth, intimacy, and personal pastness). Viewed in terms of episodic criteria, his mental states presented content adhering to the original episodic criteria, but divorced from autonoetic awareness.

This particular type of memory impairment—recollection absent a sense of personal ownership—is a form of memory dissociation that, to my knowledge, has not previously been documented in the amnesic literature (Klein and Nichols, 2012). There are, however, two cases that bear similarity. One is from a study of an amnesic reported by Talland (1964). Unfortunately, the data available from that brief report, while suggesting a similar dissociation, are too limited to support strong conclusions. In the other case (touched on earlier in this paper), a patient relearned his "personal history" following a case of severe retrograde episodic amnesia spanning most of his past life (Stuss and Guzman, 1988). The patient commented that the relearned memories seemed to lack a feel of real happenings in his life. They were, to him, more like stories and facts told to him by others (which, indeed, they were!). In this sense, they were more like semantic facts about himself (e.g. Klein and Gangi, 2010; Klein and Lax, 2010) than episodic recollections: The patient knew his memories were about him, but he did not remember them as temporally and spatially acquired in the correct context (that is, when the original acts transpired). Instead, they were memories that temporally and spatially were correctly experienced as second-hand stories told to him at a particular time and place (i.e., they consisted in the recollection of information acquired following the onset of his retrograde memory loss).

So, are R. B.'s memories episodic or semantic? The reported content suggests the former, but R. B.'s reported experience suggests the latter. Almost immediately following his accident, R. B. was able to intentionally retrieve specific events temporally and spatially situated in his personal past. But, as noted, his memories were compromised in an unusual manner—retrieval of events, though fitting the standard criteria for episodic recollection (i.e., time, place, and about R. B.), were unaccompanied by a sense of personal ownership. And, absent that sense, the ability to *feel* these memories as emanating from his personal past—to mentally travel to the time in which the events represented by his current thought and images originally transpired—was lost.

Lacking the experience of personal ownership, R. B. simultaneously lost a direct, personal connection with his past. It thus appears that loss of ownership equates to an inability to draw on the resources provided by autonoetic awareness to identify the content of a current mental state as a part of one's personal history. For example, approximately 2 months following release from the hospital, R. B. offered the following description of what it is like for him to recall personal events:

"... I did not own any memories that came before my injury. I knew things that came before my injury. In fact, it seemed that my memory was just fine for things that happened going back years in the past (the period close to the injury was more disrupted). I could answer any question about where I lived at different times in my life, who my friends were, where I went to school, activities I enjoyed. But none of it was 'me.' It was the same sort of knowledge I might have about how my parents met or the history of the Civil War or something like that."

In my review of taxonomies of long-term memory, I noted that psychologists traditionally have characterized episodic recollections as temporal, spatial, and self-referential. By these criteria, R. B.'s descriptions of his memorial experience leave little doubt that they are episodic recollections, appropriately situated in time and space, rather than factual, atemporal semantic knowledge. As I also suggested, however, there is no principled reason why a semantic fact could not contain spatial, temporal and self-referential content, or be correctly referred to a person's past—albeit a past constructed inferentially rather than autonoetically given. And therein resides a puzzle. Do R. B.'s unowned memories consist in episodic content divorced from its relational connection to autonoetic awareness, or are they rather un-categorized (i.e., as episodic or semantic) content retrieved from storage but divorced from the sense of personal ownership conferred by an act of autoneotic awareness?

R. B. addresses the question directly. When asked to recall of events from his childhood he replies:

"I was remembering scenes, not facts ... I was recalling scenes ... that is ... I could clearly recall a scene of me at the beach in New London with my family as a child. But the feeling was that the scene was not my memory. As if I was looking at a photo of someone else's vacation."

All of R. B.'s memories were substantiated by third parties as valid renditions of events that actually transpired in his life. While his recollections satisfy the traditional criteria for episodic memory—time, place, and self-accompanied by clear imagistic representation of (typically) unique events (see below for additional examples)—they simultaneously exhibit an absence of experienced ownership: While he can infer that the events recalled *must* be representative of past personal experience, he does not know this by virtue of a direct, felt connection to the past. In short, he has no sense of re-living the experiences retrieved.

The absence of ownership also is evident in R. B.'s response to instructions to recall personal memories from time spent in graduate school:

"I can picture the scene perfectly clearly ... studying with my friends in our study lounge. I can 'relive' it in the sense of re-running the experience of being there. But it has the feeling of imagining, (as if) re-running an experience that my parents described from their college days. It did not feel like it was something that really had been a part of my life. Intellectually I suppose I never doubted that it was a part of my life. Perhaps because there

[3]It is important to note that ownership of one's mental states admits to several instantiations. For example one can have "perspectival" ownership of the content of a mental state. This implies only that one is aware that the experienced state is taking place in his or her mind. R. B. clearly maintains this form of ownership. By contrast, "personal" ownership is lacking in R. B. While he understands that the memories he experiences present themselves to his consciousness, he does not feel as though they are his own. Lacking this form of ownership, he is unable to autonoetically experience the content of his mental states as expressly referring to events from his past. For detailed discussions of forms of ownership, see Albahari (2006) and Locke (1968).

was such continuity of memories that fit a pattern that lead up to the present time. But that in itself did not help change the feeling of ownership."

He continues:

"Things that were in the present, like my name, I continue to own. Having been to MIT had two different issues . . . my memories of having been at MIT I did not own. Those scenes of being at MIT were vivid, but they were not mine. But I owned 'the fact that I had a degree from MIT'. . . that might have simply been a matter of rational acceptance of fact."

Once again, R. B.'s memory performance adheres to the traditional definition of episodic recollection: He can vividly remember where the specific event transpired, when the specific event took place, and that it directly involved him. But, autonoetic awareness is missing. In short, on the view presented here, the notions of episodic and semantic can be seen to refer not to different stores or systems of memory content, but rather to how that content, once retrieved, is acted on by mechanisms (inferential or autonoetic) to enact a reference to one's past (note: not all memory content can be mapped to the past[2]). This proposal is reflected in the way R. B. treats his perspectival, but not personally, owned pre-injury memory content, both during its separation from autonoetic awareness and following their eventual recoupling—at which point memory retrieval previously experienced as "unowned" takes on a decidedly episodic flavor:

SBK: "Can you recall personally important events from your pre-injury period?"

RB: "I remember things that came before my injury. In fact, it seems that my memory is just fine for things that happened going back years in the past. I can answer questions about where I lived at different times in my life, who my friends were, where I went to school, activities I enjoyed . . . but . . . to clarify . . . I am remembering scenes, not facts. Since I am remembering scenes, I think this means I am dealing with exactly what you are asking about."

SBK: "Can you recall who you are? More specifically, what you were like and what you are like—that is, your trait characteristics. If so, are your traits felt as your own?"

RB: "Yes, I know what I am like . . . intelligent, shy, honest, a good person, things like that? Yes, I definitely have no identity problem. And the memories created since the injury I have full ownership of."[4]

SBK: "Can you recall for me a personal event concerning your time at college that would involve knowing what happened to you as a personal experience. Or is the recall more of a factual nature?"

RB: "I can see the scene in my head. I'm studying with friends in the lounge at my residence hall. I am able to re-live it. I have a feeling . . . a sense of being at there, at MIT, in the lounge. But it doesn't feel like I own it. It's like I'm imagining, re-living the experience but it was described by someone else."

SBK: "Can you recall memories whenever you desire to do so?"

RB: "I can recall memories (from the non-ownership period of his life) at will. I have normal control over remembering facts and scenes from my past. But when I remember scenes from before the injury, they do not feel as if they happened to me—though intellectually I know they did—they feel as if they happened to someone else."

With respect to the recovery of episodic ownership:

"When I did 'take ownership' of a memory, it was actually quite isolated. A single memory I might own, yet another memory connected to it I would not own. It was a startling experience to have no rhyme or reason to which memories I slowly took ownership of, one at a time at random over a period of weeks and months."

He continues:

"What happened over the coming months . . . was interesting. Every once in a while, I would suddenly think about something in my past and I would 'own' it. That was indeed something 'I' had done and experienced. Over time, one by one, I would come to 'own' different memories. Eventually, after perhaps 8 months or so, it seemed as if it was all owned . . . as if once enough individual memories were owned, it was all owned. For example, the MIT memory, the one in the lounge . . . I now own it. It's clearly part of my life, my past."

SUMMING UP: THE CASE OF PATIENT R. B. AND ITS IMPLICATIONS FOR EPISODIC MEMORY

There appears to be an intimate connection with, and possibility of separation between, the content of a memory experience and whether that experience is autonoetic. R. B.'s confusion with regard to "content ownership" highlights the intimate relation between autonoetic awareness and ownership: Absent a sense of ownership, R. B. cannot mentally travel back in time to claim as his own the re-presentation of the experience from which the occurrent content was derived. Instead he relies on inference and logical possibility to (often correctly) infer that, given the specific elements of the content retrieved, it likely represents aspects of his personal past.

The apparent paradox presented by the case of patient R. B.—episodic-like content absent the feeling of personal ownership (and thus lived pastness)—can be understood by situating episodic memory in the context of a system of interrelated memory processes, some of which provide the raw data for experience (i.e., content) and some of which enable the experience to be "mine" (for extended treatments, see Klein, 2004, 2010, 2012; Klein et al., 2004; Klein and Nichols, 2012). R. B.'s recollections during his "unowned" period can be explained in the context of the view that there is specialized neural machinery that acts on retrieved content (of the right sort; e.g., Footnote 2) to confer on it a *sense* of re-living a personal experience—i.e., episodic recollection. This neural machinery in R. B. seems to have been compromised by his injury, but only for those events that occurred in the time period preceding his injury. That is, R. B. suffered a form of retrograde amnesia that compromised his ability to experience his personal recollections as his own. During the non-ownership period, R. B. had memory of pre-injury events and could locate

[4]Note that despite his ownership/autonetic limitations, R. B.'s responses exhibit a clear sense of self both narratively and factually. Thus, it is reasonable to conclude that his memory issues are not traceable to impairments of self (Klein et al's, 2004, subsystem #1). In addition, throughout his period of impairment he exhibits a clear and precise ability to perform a requested retrieval, thus demonstrating intact agency with regard to memory (which suggests, in turn, that subsystem #2 has not unduly been impacted by his injuries). That he has an intact sense of agency also can be seen from his remarks as the interview continues.

them, via inference, in his personal past. But he lacked a sense of numerical personal identity with the experiences retrieved. The case of R. B. thus suggests that the sense of numerical personal identity is quite narrowly circumscribed: R. B. had factual self-knowledge, trait self-knowledge, and knowledge of personally experienced episodes, but he did not have a pre-reflectively given sense of continuity with his past person.

Importantly, during his "unowned" period R. B. had no trouble retrieving very specific, often one-of-a kind, personal experiences (e.g., being on a beach in New London). He presumably also had no trouble representing that his body was present for those experiences. He *knew* that the memories were about him rather than, say, his mother. And he could call up, that is, auto-cue (Donald, 1991) memories at will. So, in that sense, his memories were both agentic and involved self-reference. However, there seems to be another type of self-reference that typically accompanies episodic recollections (ownership, mineness; for discussion, see Klein, 2012) that has been impaired in his case. His apparent deficit was in representing, from the first person, "I had these experiences." That is, his impairment entailed a loss of the ability to connect personally experienced content with autonoetic awareness.

A MECHANISM: ONE PROPOSAL

Although the specifics of R. B.'s deficit are, at this point, unclear, it is worth considering the present findings in light of theoretical work by Dalla Barba and colleagues (e.g., Dalla Barba, 2002; Dalla Barba et al., 1997, 1999) on the relation between consciousness, memory, and temporal experience. These authors call attention to two modes of consciousness, which they term temporal consciousness (TC) and knowing consciousness (KC). TC is consciousness of time—it enables a person to become aware of something as part of his or her personal past, present, or future. It thus corresponds closely to what Tulving calls autonoetic awareness. KC, by contrast, does not locate objects in time. Rather, it enables a person to become aware of something as an element of knowledge without that knowledge being situated in a temporal framework. The conceptual overlap with noetic awareness is evident.

TC and KC thus conceptualized are two different ways of *addressing* the contents of memory. Long-term memory is held to contain representations that vary in terms of their stability and resistance to modification (e.g., Dalla Barba et al., 1997, 1999; Nadel and Moscovitch, 1997). The more stable, overlearned, summary representations can be thought of as roughly analogous to what *will be* experienced, on retrieval, as semantic knowledge, whereas less stable, more malleable representations—e.g., unique, one-of-a-kind-events—provide the raw material for what will subsequently become episodic recollection.

Support for these proposed distinctions in content stability can be found in Nadel and Moscovitch's (1997; Moscovitch et al., 2005) multiple trace theory (MTT) of long-term memory consolidation (see also Piolino et al., 2003). According to MTT, the hippocampal formation and related structures (primarily in the medial temporal lobes) contribute to the transformation of initially unstable and sparsely encoded content into a collection of contextually related traces—a transformative act that confers stability on represented content by virtue of its multiple instantiations. The model, developed to map the neural events and structures underlying the transition of information from episodic to semantic memory (i.e., unstable to stable), fits reasonably well with Dalla Barba's proposal that differences in representational stability determine whether a given memory content will be taken an as object by TC and KC.

But, in what sense does the relative stability (or a lack thereof) confer a temporal status on a specific content? That is, what determines if the content, as experienced, is classified as episodic or as semantic? Dalla Barba (2002) suggests that the stability of a representation is correlated with what we typically describe as episodic memory by virtue of the fact that TC takes such content as its intentional object (for a discussion of why this may be the case, see Klein et al., 2002a). In this way, temporally and representationally unique events are likely to be experienced episodically as part of one's past. By contrast, the memory content psychologists classify as semantic often, though not invariably, tends to be represented as stable, summaries of (often repeated) experiences that share features in common. While such content is acted on by KC rather than by TC (i.e., autonoetic awareness), there is nothing in Dalla Barba's model that precludes KC (i.e., noetic awareness) from recruiting an individual's logical abilities to inferentially place "stable" content in a temporal context, provided the representation being addressed contains temporally-relevant constituents. When this happens, the individual is able to locate well-learned, multiply-represented facts about the world in a temporal matrix that extends from the chronological past to the chronological future (e.g., "I know I lived in New York until I was 2 years old, even though I can't recollect any specific event from that time of my life").

Unfortunately, as the reader will have noted, Dalla Barba's "explanation" begs the question of what *causes* the observed correlation between type of temporal subjectivity and stability of content. At present, a compelling explanation is not readily at hand. Despite its conceptual limitations, however, Dalla Barba's model, in conjunction with MTT, provides a provisional (though incomplete) framework for making sense of the dissociation between the experiential and inferential forms of temporality experienced by patient R. B. As the result of a condition in which autonoetic awareness is intact, but unable to access pre-injury content in long-term memory, R. B. remains capable of describing, often in considerable detail, what happened in his pre-injury past—despite being unable to experience his present mental content as a re-living of past personal events. By contrast, autonoetic awareness still can, for reasons not clear, successfully work in conjunction with his post-injury memory content. What we see in the case of R. B. is not a failure of memory content, or a loss of the autonoetic component of recollection, but rather a dissociation between two intact, yet functionally independent, constituents of what, taken in tandem, are essential constituents of what we classify as episodic recollection.

The merit of this explanation of the relation between content and experience is further supported by R. B.'s subsequent recovery of the ability to episodically recollect the *same* memory content that lacked personal ownership during the period of his cognitive impairment. That R. B. was able to regain these

functions suggests that the autoneotic aspect of his recollections was not destroyed by his injury; rather it temporarily became decoupled from memory content. The proposition that the mechanisms mediating autonoetic awareness were not lost during his amnesia also is implied by the fact that he had a sense of personal ownership of ongoing experiences that transpired *following* his accident (with the exception of temporally limited anterograde memory loss). Why his mental machinery was able to conjoin autonoetic awareness with content as memories were being built, but not when recollecting memories of pre-injury events, remains unclear.

CONCLUSIONS

The sense of a direct, pre-reflective attachment to the past given by episodic recollection is robust, indeed, it has seemed to many to be a necessary aspect of episodic memory (for reviews, see Tulving, 1985, 2002; Wheeler et al., 1997). It also gives us an "irresistible" sense of being the same person over time (e.g., Fivush and Haden, 2003; for discussion, see Klein, 2013b). But the case of R. B. indicates that this sense is dissociable from memory content. The feeling of autonoetic personal continuity (and its intimate relation to personal ownership) turns out to be a contingent feature of memory content that comes into play at retrieval.

Seen in this light, classification of content as episodic or semantic can be situated in processes that transpire once memory content is retrieved and made available for conscious experience. It is at this point that the designators episodic and semantic do the work they were developed to perform. This work is achieved via the individual's ability to connect a current mental state to a past experience via either autonoetic awareness (temporarily lost in R. B, but subsequently regained) or logical inference. The former maps to what we call episodic memory, while the latter enables temporally located semantic knowledge—i.e., the intentional placement of retrieved content in the context of one's past (provided the content has useable temporal, spatial and self-referential markers).

Of course, R. B.'s reports do not rule out the possibility that what he is reporting are inferences based on semantic memory system (as his responses make clear, he is capable of inference) rather than "un-labeled" memory content that lacks a felt connection to his past due to compromised autonoetic awareness. However, this possibility assumes that semantic memory is a system whose instantiation is a biological reality *prior to* an act of retrieval—a conceptual stance which theoretical and empirical observations presented in this paper call into question. Moreover, Occam's principle of parsimony—i.e., posit no more parameters or variables than are minimally necessary to account for the data (e.g., Ladyman, 2002)—appears to side with the view that memory content is classifiable neither as episodic or semantic while still in storage. Of the two possibilities under discussion, the retrieval-based alternative offers the simpler explanation—positing a single source of content that can be differentially acted on by autonoetic awareness. By contrast, the traditional classification of episodic and semantic memory as unique, but interacting, neuro-cognitive systems assumes two separate repositories of content (episodic *and* semantic) which *also* are differentially associated with autonoesis.

Occam's razor resonates with evolutionary considerations as well. Evolution builds on existing biological structures (e.g., Williams, 1966). Consistent with this thesis, Fuster (1995) has demonstrated a strong overlap among humans and phylogenetically older mammalian species in the cortical areas involved in memory. Accordingly, positing a pre-existing cortical network of memory content that subsequently was overlain with mechanisms that acted differentially on retrieved content to enable conscious experience to be taken as either episodic or semantic has economically favorable consequences. Specifically, it has the effect of eliminating the need to posit the evolution of separate systems of storage for episodic and semantic content, as well as separate mechanisms (i.e., autonoetic and noetic) for consciously experiencing that content as episodic recollection or semantic knowledge.

These considerations also offer an evolutionary perspective on the well-known finding that some species (e.g., scrub jays), lacking some of the structures assumed necessary for episodic recollection (e.g., personal ownership, sense of self), nonetheless behave *as though* their acts were mediated by recollection (e.g., Cheke and Clayton, 2010). Such behavior can parsimoniously be explained by assuming these species have a network for storing memory content, some which contains information about time and place, but have yet to evolve the mechanisms necessary to place that content into subjective alignment with their personal past. Thus, they can use their knowledge to appropriately guide behavior without that knowledge being experienced as part of their personal past.

The retrieval-based model of episodic and semantic memory also may help explain the well-known finding that the *experience* of remembering often is characterized by either a feeling of knowing or a feeling of remembering (for reviews, see Cohen et al., 2008 and Gardiner and Richardson-Klavehn, 2000). A popular dual systems explanation for variation in modes of retrieval experience is that feelings of remembering reflect the operation of episodic memory whereas the feelings of familiarity are associated with semantic memory (e.g., Tulving, 1985).

In contrast to dual systems analyses, a retrieval-based model proposes that whether content retrieved from memory is experienced as remembered or as known depends on whether it has been subject to autonoetic consciousness: If it has, the content is experienced as remembered; if not, it is experienced as known. This explanation has the advantage of avoiding the problem (common to dual systems models) of explaining why stimuli encoded under the *same* temporal and spatial conditions are stored in, and subsequently retrieved from, one system vs. another. A retrieval-based model posits that all stimuli are stored in the same neural system; any difference in mode of presentation pivots on whether or not content is acted on by autonoetic awareness at retrieval.

Although this model has the advantage of conceptual and phylogenetic parsimony (e.g., a single system of storage), an obvious limitation is that identification of the factors responsible for whether retrieved content will be subject to autonoetic embellishment is, at present, unknown. However, a similar indictment can be pressed against most *process*-based explanations of the remember/known phenomenon. Regardless of whether one subscribes to a dual or single process explanation (e.g., Tulving, 1985; Gardiner

and Java, 1990; Donaldson, 1996; Wixted and Mickes, 2010; for review see Cohen et al., 2008), there is no compelling a priori basis for linking variations in autonoetic awareness to the potency of causally-relevant factors (such as trace strength, fluency, decision criteria, and automaticity); rather, these processes are invoked post hoc to explain observed variation in participants' retrieval phenomenology.[5]

At present, there is no conclusive theoretical or empirical evidence to select between a systems-based and retrieval-based explanation of the episodic/semantic distinction (I address the untidy nature of neural localization studies of memory in the next section). Occam's principle, while supportive of a retrieval-based view, is best treated as a logically non-binding heuristic rather than as a definitive arbiter of theoretical substantiation. Compelling empirical evidence in support of a retrieval-based interpretation comes from the fact that, on recovery of his sense ownership, the same content formerly unconnected to R. B.'s personal past re-acquired a sense of being an episodic recollection. While definitive evidence for a retrieval-based theory of episodic and semantic memory is not available at present, R. B.'s memory performance, taken in conjunction with considerations of parsimony and evolution, suggest this option should be considered a live possibility.

THE NEURAL LOCALIZATION OF EPISODIC AND SEMANTIC MEMORY

The localization of episodic (and semantic) memory in their neural substrates has been a task that has captured the interest of neuro-imagers for several decades (for reviews, see Squire, 2004; Moscovitch et al., 2006; Martinelli et al., 2012; Renoult et al., in press). However, despite guarded optimism initially expressed that the goal of localization of the relevant networks was "in sight" (e.g., Nyberg et al., 1996), the complexities underlying these early forays soon became evident. Researchers were led to conclude that the networks associated with episodic and semantic memory are widely distributed in the brain (e.g., the parietal lobes, the frontal lobes, medial temporal lobes; e.g., Nyberg and Tulving, 1998; Moscovitch et al., 2005; Wagner et al., 2005; Burianova and Grady, 2007; Squire and Bayley, 2007; Cappa, 2008; Ryan et al., 2008; Eichenbaum et al., 2012; for review, see Svoboda et al., 2006; Uttal, 2009), that their boundaries were fluid, and that their constituents varied as a function of the task performed, content retrieved, and a host of related factors such as the individual's age, handedness, gender, clinical status, and emotional state (e.g., Achim and Lepage, 2003; Bartha et al., 2003; Schwindt and Black, 2009; Smith and Squire, 2009; for review, see Dumit, 2004). Not surprisingly, even the manner in which constructs of interest were operationalized had important effects on the cortical regions activated (e.g., Renoult et al., in press). One might argue that there is as much evidence for the incoherence of the underlying constructs as there is for the complexities of the issues involved in designing studies, analyzing data and interpreting findings from brain-mapping endeavors (e.g., Uttal, 2001).

A possible reason for the diversity of imaging results is that episodic memory is not something to be neurally localized—it is not a *thing* to be found. Rather, it consists in a collection of functionally independent, but normally interacting functions (e.g., Klein, 2001; Klein et al., 2004), which, as the present study demonstrates, can differentially be impaired due to neurological damage (for reviews, see McCarthy and Warrington, 1992; Klein et al., 2004). As Polanyi (1967) cautioned "... either you know what you are looking for, and then there is no problem; or you do not know what you are looking for, and then you cannot expect to find anything" (p. 22).

Despite the difficulties of the enterprise, there are several conclusions that can provisionally be drawn from studies imaging episodic and semantic memory. Of particular relevance to present considerations, a number of labs have converged on the medial temporal lobes as a common network underlying episodic and semantic consolidation and storage (e.g., Scoville and Milner, 1957; Achim and Lepage, 2003; Bartha et al., 2003; Piolino et al., 2003; Levy et al., 2004; Moscovitch et al., 2005; Svoboda et al., 2006; Ryan et al., 2008; Smith and Squire, 2009; Naya and Suzuki, 2011; Rosenbaum et al., 2012; Eichenbaum et al., 2012). In addition, these networks also are implicated in the consolidation and storage of declarative memory content (for review, see Fuster, 1995; Squire, 2004). While highly speculative, I suggest that these regions of activation may reflect the storage of memory content prior to its subsequent demarcation as semantic and episodic via mechanisms acting at retrieval. By contrast, a number of investigators have suggested that autonoetic awareness depends on mechanisms residing primarily in the frontal lobes (e.g., Abraham et al., 2009; for reviews, see Wheeler et al., 1997; Szpunar, 2011; Tulving and Szpunar, 2012).

THE EPISODIC/SEMANTIC DICHOTOMY AND DECLARATIVE MEMORY

An implication of my proposal, in partial agreement with Squire and his colleagues, is that cortical separation of memory systems may better be captured by a declarative/procedural dichotomy (where episodic and semantic systems are folded into, rather than constituents of, declarative long-term memory; e.g., Cohen, 1984; Squire, 2004) than by a taxonomy in which episodic and semantic memory are seen as conceptually and neurologically distinct constituents of the declarative system (e.g., Schacter and Tulving, 1994; for discussion, see Foster and Jelicic, 1999).

But—and this is an important caveat—my concession to the declarative/procedural model comes at the level of the neural instantiation of memory content, not at the level of phenomenology once that content has been retrieved and made available

[5]To quote Bartlett (1932), the processes invoked "... may show us what can happen when recognition takes place, but throw no light whatever upon how any, or all, of these processes are rendered possible ... experimenters have analyzed the final stage of recognition and each has tended to claim a complete solution in terms of his particular analysis. In fact, nobody can understand recognition by confining his attention to what happens at the moment of recognition." (p. 192). Bartlett goes on to say that future experimentation focusing on the mental events that precede recognition will aid in understanding variability in the processes subsequently at work. If one substitutes retrieval (e.g., recall and recognition) for recognition, the quote from Bartlett perfectly captures my critique of process-based explanations of the remember/know phenomenon. This critique applies to my retrieval-based proposal as well: As it currently stands, a retrieval-based model cannot account for variability in the attachment of autonoetic awareness to memory content. This is not cause for dismay; rather, as Bartlett notes, it simply points out the need for further experimentation designed to clarify how the processing differences apparent at retrieval are put into place.

as an object for subjectivity. Accordingly, the episodic/semantic division of long-term memory is not subsumed by declarative memory (as Squire and colleagues might argue); rather, the episodic/semantic division of memory comes into play at the level of retrieval rather than storage.

This view can accommodate several conflicting findings in the literature. For example, while some clinical dissociations between intact and impaired memory function appear best classified in terms of a functional independence of episodic and semantic memory (for reviews, see Schacter and Tulving, 1994; Klein, 2004, 2010; Dere et al., 2008), other results do not fit as neatly into this scheme (e.g., Cohen, 1984; Squire, 1987; Kopelman et al., 1989; Klein et al., 2002c). In fact, an unambiguous sorting of spared and preserved function into the categories provided by the episodic/semantic distinction more often is the exception than the rule (e.g., Squire, 1987; Baddeley et al., 1995; Parkin, 1997; Foster and Jelicic, 1999; Klein et al., 2002c; Moscovitch et al., 2006).

However, recognition of the possibility that an episodic/semantic classification of memory impairment is attendant on contingencies acting at retrieval can accommodate the diversity of results. Specifically, impairments acting primarily on stored content may result in impairments to *both* episodic and semantic memory experience, whereas separation between these two forms of memory phenomenology is more likely to be observed when neuro-cognitive impairments act on the mechanisms operative during retrieval.

Evidence for this proposal comes from the case of patient D. B., who suffered brain damage as a result of anoxia following cardiac arrest (e.g., Klein et al., 2002b,c). Neuropsychological assessment of D. B.'s temporal orientation showed severe disorientation with respect to the present. For example, he did not know the day of the week, the current year, or even his age. Additional testing revealed that D. B. was unable to recall his past and unable to imagine what his experiences might be like in the future (for review, see Klein, 2013b). Not surprisingly, D. B.'s episodic memory was severely impaired: He could not reliably bring to mind personal experiences from any point in his past (at least within the limits of testing). By "reliably" I mean the while D. B. typically responded to requests for episodic memories with "I don't know," he occasionally did offer a specific "recollection." However, these "recollections" lacked rational placement in his past. For example, in response to the request that he remember a time he was in a car, D. B. replied "Driving down the coast with my parents." When then asked to temporally place the memory, he replied "yesterday," despite his parents having been dead for 34 years! Thus, an occurrent mental state (the content of which was verified by his daughter) appears to have broken free of its temporal moorings. That is, the content of memory, absent autonoetic temporal placement, constituted the object of D. B.'s awareness.

What I am arguing is that patients such as R. B. and D. B. may suffer from a disruption of autonoetic awareness, and that as a result of this pathology they are rendered unable to experience mental content in its proper temporal context (for a similar views, see Tulving, 1985; Dalla Barba, 2002). It is the failure to connect autonoetic awareness with retrieved content rather than the absence of such awareness, that accounts for (at least some) of the memory pathologies demonstrated by amnesic patients.

This is not to presume that all forms of episodic amnesia submit to similar analysis. Memory loss can result from failures at encoding, storage and/or retrieval. One could, for example, present symptoms consistent with episodic amnesia if s/he maintained the requisite mechanisms for temporal subjectivity, but lacked access to the content on which that awareness could be brought to bear. Content loss can be highly selective. According to MTT, less stable (and hence more autonoetically-relevant) content is likely to be under-represented in memory. It thus is more susceptible to neural insult than are the more richly distributed representations that ultimately will constitute semantic memory experience (e.g., Nadel and Moscovitch, 1997). In this way, episodic amnesia will manifest more readily than sematic amnesia (as is well-recognized to be the case)—the result of disease processes acting on content storage prior to operations taking place at retrieval. What I am suggesting, then, is that some (though certainly not all!) forms of amnesia can arise from the decoupling of temporal awareness and memory content (for a similar view, see Tulving, 1985).

Another area of research that submits to a retrieval-based analysis is the debate surrounding the mechanisms underlying false memories (for review, see Schacter, 1995; Johnson and Raye, 1998). According to the present model, memory errors can result when (1) compromised content is taken as the object of autonoteic awareness as well as (2) when autonoetic awareness is misapplied (e.g., to imagination). The phenomenon of implicit task performance also can be explained (in some cases) as the failure of autonoetic awareness to place memory content in a temporal context. While both of these phenomena (false and implicit memory) deserve considerably more attention, restrictions of space prevent further elaboration.

LIMITATIONS AND CONSIDERATIONS

An issue raised concerning the model I have presented is that it seems more a philosophical exercise that a scientific theory. Concern centers on the fact that evidence in support of my ideas derives primarily (though not exclusively: e.g., patient D. B, thought insertion) from the study of a single patient (R. B.) who now has remitted. Accordingly, it is hard to see how the ideas I have proposed can be tested via experimental manipulation. There are several things to note in this regard.

First, not all theory-based scientific enterprises admit to empirical *manipulation* (e.g., cosmology, paleontology). While the potential for refutation is essential (e.g., Popper), refutation does not mandate explicit manipulation in an experimental context (e.g., Trusted, 1987; Lipton, 1991). A good theory is one that retrodicts and predicts, both of which afford the potential for refutation in the absence of the ability to directly manipulate variables of interest.

Second, a good theory facilitates the organization of data sets that might otherwise have been viewed as collections of unrelated findings (e.g., Newell, 1973; Ladyman, 2002; Godfrey-Smith, 2003). Along these lines, the present theory has the virtue of offering a parsimonious explanation for a variety of "apparently" diverse memory phenomena, including, but not limited to, remember/know judgments, the implicit/explicit memory distinction, false memories and Déjà vu experience

(to be discussed in a forthcoming paper). It also can account for the fact that some individuals suffering Dissociative Identity Disorders experience the *same* episodic content (e.g., Dorahy, 2001) despite content ownership varying as a function of the personality currently occupying awareness (e.g., Braude, 1995). The theory also accounts for the fact that episodic and semantic content evidence significant (often indistinguishable) overlap with regard the presumably differentiating features of time, place and self (e.g., Klein and Lax, 2010).

Third, the availability of theory can help to draw attention to neurological case studies whose relevance for the study (in this case, of memory) has, to date, been underappreciated. For example, Zahn et al. (2007) report the case of a patient D. P., who lost his ability experience ownership of the mental states accompanying perceived objects. In a case described by Gott et al. (1984), the patient (J. J.) was capable of holding either of two qualitatively different states of consciousness. Specifically, she was voluntarily able to switch between the feeling that her experiences belonged to her or to someone else. Finally, a patient described by Sass and Parnas (2003) reported that his feeling ownership accompanying his mental states lagged behind his initial awareness of those states. This "phenomenological delay in felt ownership" suggests that ownership is a separable component of consciousness—i.e., the patient temporarily was aware of having an experience, but only subsequently felt that his first-person perspective belonged to him.

Taken together, these studies focus attention on ownership as an aspect, or form, of consciousness that can come undone under certain conditions (e.g., Klein and Nichols, 2012; Lane, 2012). With respect to the theory of episodic memory I have proposed, these studies potentially constitute a small data-base (I suspect additional cases will appear in the literature if dysfunction of content ownership becomes a recognized issue in memory research) that, once assembled, will permit investigators to empirically test the effects of "loss of ownership" on memorial experience.

Fourth, as things currently stand, my theory also submits to empirical testing with *non*-impaired participants. Here I outline one such study (others will be discussed in a forthcoming paper). Assuming it possible to *simultaneously* achieve a high degree of temporal and spatial resolution using various brain scanning technologies (e.g., EEG, fMRI, and PET) it should be feasible to track both the chronology and localization of neural activity during performance of a "remember/know" task. If temporal resolution is sufficiently sensitive, and the constructs in play sufficiently well defined (note: "sufficiently" may require technological and conceptual refinement), it would allow us to examine the stages of memory (i.e., encoding, storage, and retrieval) activated during the process of declarative remembering. Anatomical localization—in conjunction with "stage" information provided by temporal data—would enable us to bring to focus the systems responsible for storage (which are, of logical necessity, causally prior to retrieval) followed by those involved in retrieval. If my model has merit, the activation of stored content during performance of the remember/know task will evidence comparable localization(s) regardless of whether the participant's phenomenological report turns out to be "remember" or "know." Neural separation, by contrast, should be evidenced during the retrieval phase (due to differences in the mechanisms mediating remember/know judgments—i.e., inference vs. autonoetic awareness).

Finally, the notion that single case studies have serious limitations with regard to theory construction is far from agreed on. In fact, Caramazza (1986, 1991) and Sokol et al. (1991) have argued persuasively for the importance of $N = 1$ studies in the development of neuropsychological models. Of course, not everyone shares this view: Some feel that theory construction requires inference from group performance (e.g., Shallice, 1988; Robertson et al., 1993). However, since there are no "knockdown" arguments favoring one view to the exclusion of the other, there is, at present, no logically compelling reason for conceptual closure.

The theory presented herein also offers a potential corrective on research practices that may be doing more to cloud than to illuminate the role of long-term memory in various task performances. A central idea of this paper is the episodic and semantic memories are distinguished not by their content, but rather by the way that content is phenomenologically given: The features of "episodic content" are not, in principle, distinguishable from those of "semantic content." This calls into serious question the advisability of studies attempting to document the workings of a particular type of declarative memory via analysis of reported remembered content. To take one example (and there are a multitude), a recent paper by Rasmussen and Bernsten (2012) attempts to document the episodic contributions to future-oriented thought by examining the relative proportions of episodic and semantic content present in participants' memory transcripts. Such an attempt, on present considerations, is misguided since there is no principled way in which a researcher can classify content as episodic or semantic; the episodic and semantic designationors refer to the manner in which content is experienced at retrieval.

FINAL THOUGHTS

The present emendation of the episodic/semantic memory distinction awaits the considerable work of empirical conformation and theoretical accommodation. However, despite its provisional status, it has the merit of (1) being consistent with real-world data from case studies (e.g., R. B., and D. B.), (2) helping bring some order to the debate over whether episodic and semantic memory are best construed as functionally independent neural systems, or rather two ways scientists (though not necessarily nature) have chosen to divide up declarative memory, (3) helping make sense of impairments in mental time travel (both into the past and future; for discussion, see Klein, 2013a), (4) accommodating a number of findings (e.g., the differential bases for, and forms of, episodic amnesia, memory errors, and performance on implicit memory tasks), and (5) having considerations of parsimony (both logical and evolutionary) on its side.

The decoupling of autonoetic awareness and memory content—revealed most clearly by the case of R. B. (see also the case of patient D. B)—can be taken as an "existence proof" for the proposition that the connection between autonoetic awareness and episodic memory is one of contingency rather than one of necessity. That is, R. B.'s memory phenomenology suggests that awareness is not an *intrinsic* property of episodic content; rather,

the association between content and awareness may best be construed as a *relation* between two functionally independent systems that jointly contribute to the experience of episodic recollection.

Perhaps ironically, Hermann Ebbinghaus, a name typically associated with an approach to memory now discredited as being overly-influenced by logical positivism (e.g., Bartlett, 1932; Danziger, 2008), seems to have intuited (though not explored) the need to invoke acts of consciousness to explain memory phenomenology. In the introductory remarks in his book *Memory*, Ebbinghaus makes the following observation: ". . . in the majority of cases we at once recognize the returned mental state as one that has already been experienced; that is, we remember it. Under certain conditions, however, this *accompanying* consciousness is lacking and we know only indirectly that 'now' must be identical with 'then'. . . " (Ebbinghaus, 1885/1913, p. 2; emphasis mine). Put in terms of the model proposed in the present paper, Ebbinghaus is calling attention to the need to posit an autonoetic-like form of consciousness that acts on retrieved memory content to provide the experience of pastness as directly given (i.e., episodic) rather than indirectly inferred (i.e., semantic).

REFERENCES

Abraham, A., Schubotz, R. I., and von Cramon, Y. (2009). Thinking about the future versus the past in personal and non-personal contexts. *Brain Res.* 1233, 106–119.

Achim, A. M., and Lepage, M. (2003). Episodic memory-related activation in schizophrenia: a meta-analysis. *Br. J. Psychiatry* 187, 500–509.

Albahari, M. (2006). *Analytical Buddhism: The Two-Tiered Illusion of Self.* Houndsmills: Palgrave Macmillan.

Baddeley, A. D., Wilson, B. A., and Fraser, N. W. (1995). *Handbook of Memory Disorders.* New York, NY: John Wiley and Sons.

Bartha, L., Brenneis, C., Schocke, M., Trinka, E., Koylu, B., Trieb, T., et al. (2003). Medial temporal lobe activation during semantic language processing: fMRI findings in healthy left- and right-handers. *Cogn. Brain Res.* 17, 339–346.

Bartlett, F. C. (1932). *Remembering.* London: Cambridge At The University Press.

Bernecker, S. (2010). *Memory: A Philosophical Study*. Oxford: Oxford University Press.

Bortolotti, L., and Broome, M. (2009). A role for ownership and authorship in the analysis of thought insertion. *Phenomenol. Cogn. Sci.* 8, 205–224.

Braude, S. E. (1995). *First Person Plural: Multiple Personality and the Philosophy of Mind.* Lanham, MD: Rowman and Littlefield Publishers.

Burianova, H., and Grady, C. L. (2007). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *J. Cogn. Neurosci.* 19, 1520–1534.

Cappa, S. F. (2008). Imaging studies of semantic memory. *Curr. Opin. Neurobiol.* 21, 669–675.

Caramazza, A. (1986). On drawing inferences about the structure of normal cognitive systems from the analysis of patterns of impaired performance: the case for single-patient studies. *Brain Cogn.* 5, 41–66.

Caramazza, A. (1991). Data, statistics, and theory: a comment on Bates, McDonald, MacWhinney, and Applebaum's "A maximum likelihood procedure for the analysis of group and individual data in aphasia research". *Brain Lang.* 41, 43–51.

Casey, E. S. (1977). Imagining and remembering. *Rev. Metaphys.* 31, 187–209.

Cheke, L. G., and Clayton, N. S. (2010). Mental time travel in animals. *WIREs Cogn. Sci.* 1, 1–16.

Cohen, A., Rotello, C., and MacMillan, N. (2008). Evaluating models of remember-know judgments: complexity, mimicry, and discriminability. *Psychon. Bull. Rev.* 15, 906–926.

Cohen, N. J. (1984). "Preserved learning capacity in amnesia: evidence for multiple memory systems." in *Neuropsychology of Memory,* eds L. R. Squire and N. Butters (New York, NY: Guilford Press), 83–103.

Dalla Barba, G. (2002). *Memory, Consciousness and Temporality*. Norwell, MA: Kluwer Academic Publishers.

Dalla Barba, G., Cappelletti, J. Y., Signorini, M., and Denes, G. (1997). Confabulation: remembering another' past, planning? another' future. *Neurocase* 3, 425–436.

Dalla Barba, G., Nedjam, Z., and Dubios, B. (1999). Confabulation, executive functions, and source memory in Alzheimer's disease. *Cogn. Neuropsychol.* 16, 385–398.

Danziger, K. (2008). *Marking the Mind: A History of Memory*. Cambridge: Cambridge University Press.

Dere, E., Easton, A., Nadel, L., and Huston, J. P. (eds.). (2008). *Handbook of Episodic Memory.* Amsterdam: Elsevier Science.

Donald, M. (1991). *Origins of the Modern Mind: Three Stages in the Evolution of Culture and Cognition*. Cambridge, MA: Harvard University Press.

Donaldson, W. (1996). The role of decision processes in remembering and knowing. *Mem. Cogn.* 24, 523–533.

Dorahy, M. (2001). Dissociative identity disorder: disorder and memory dysfunction: the current state of experimental research and its future directions. *Clin. Psychol. Rev.* 21, 771–795.

Dumit, J. (2004). *Picturing Personhood: Brain Scans and Personal Identity*. Princeton, NJ: Princeton University Press.

Ebbinghaus, H. (1885/1913). *Memory: A Contribution to Experimental Psychology.* Translated eds H. A. Ruger and C. Bussenius (New York, NY: Teacher's College, Columbia University).

Eichenbaum, H., Sauvage, M., Fortin, N., Komorowski, R., and Lipton, P. (2012). Towards a functional organization of episodic memory in the medial temporal lobe. *Neurosci. Biobehav. Rev.* 36, 1597–1608.

Fivush, R., and Haden, C. A. (eds.). (2003). *Autobiographical Memory and the Construction of a Narrative Self*. Mahwah, NJ: Lawrence Erlbaum Associates.

Foster, J. K., and Jelicic, M. (1999). *Memory: Systems, Process, or Function?* New York, NY: Oxford University Press.

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. East Sussex, England: Erlbaum/Taylor and Francis.

Furlong, E. J. (1951). *A Study in Memory*. New York, NY: Thomas Nelson and Sons Ltd.

Fuster, J. M. (1995). *Memory in the Cerebral Cortex: An Empirical Approach to Neural Networks in the Human and Nonhuman Primate*. Cambridge, MA: MIT Press.

Gallagher, S. (2000). Philosophical conceptions of the self: implications for cognitive science. *Trends Cogn. Sci.* 4, 14–21.

Gardiner, J., and Richardson-Klavehn, A. (2000). "Remembering and knowing," in *The Oxford Handbook of Memory*, eds E. Tulving and F. I. M. Craik (New York, NY: Oxford University Press), 229–244.

Gardiner, J. M. (2001). Episodic memory and autonoetic consciousness: a first-person approach. *Philos. Trans. R. Soc. B Biol. Sci.* 356, 1351–1361.

Gardiner, J. M., and Java, R. I. (1990). Recollective experience in word and nonword recognition. *Mem. Cogn.* 18, 23–30.

Godfrey-Smith, P. (2003). *Theory and Reality*. Chicago, IL: University of Chicago Press.

Gott, P. S., Hughes, E. C., and Whipple, K. (1984). Voluntary control of two lateralized conscious states: validation by electrical and behavioral studies. *Neuropsychologia* 22, 65–72.

Hume, D. (1748/2004). *An Enquiry Concerning Human Understanding.* New York, NY: Dover Publications.

Husserl, E. (1964). *The Phenomenology of Internal Time-Consciousness*. Bloomington, IN: Indiana University Press.

James, W. (1890). *Principles of Psychology, Vol. 1.* New York, NY: Henry Holt and Company.

Jaynes, J. (1976). *The Origin of Consciousness in the Breakdown of the Bicameral Mind*. Boston, MA: Houghton Mifflin Company.

Johnson, M., and Raye, C. (1998). False memories and confabulation. *Trends Cogn. Sci.* 2, 137–145.

Johnson, M. K., and Raye, C. L. (1981). Reality monitoring. *Psychol. Rev.* 88, 67–85.

Johnson, M. K., Hashtroudi, S., Lindsay, D. S. (1993). Source monitoring. *Psychol. Bull.* 114, 3–28.

Klein, S. B. (2001). "A self to remember: a cognitive neuropsychological perspective on how self creates memory and memory creates self," in *Individual Self, Relational Self, and Collective Self,* eds C. Sedikides and M. B. Brewer (Philadelphia, PA: Psychology Press), 25–46.

Klein, S. B. (2004). "The cognitive neuroscience of knowing one's self," in *The Cognitive Neurosciences III*, ed M. A. Gazzaniga (Cambridge, MA: MIT Press), 1007–1089.

Klein, S. B. (2007). "Phylogeny and evolution: implications for understanding the nature of a memory system," in *Science of Memory: Concepts,* eds

H. L. Roediger, Y. Dudai, and S. Fitzgerald (New York, NY: Oxford), 377–381.

Klein, S. B. (2010). The self: as a construct in psychology and neuropsychological evidence for its multiplicity. *WIREs Cogn. Sci.* 1, 172–183.

Klein, S. B. (2011). "An evolutionary analysis of the concept of memory systems," in *Thus Spake Evolutionary Psychologists,* eds X. T. Wang and Y. J. Su (Beijing: Peking University Press), 140–157.

Klein, S. B. (2012). The self and its brain. *Soc. Cogn.* 30, 474–516.

Klein, S. B. (2013a). The complex act of projecting oneself into the future. *WIREs Cogn. Sci.* 4, 63–79.

Klein, S. B. (2013b). The sense of diachronic personal identity. *Phenomenol. Cogn. Sci.* doi: 10.1007/s11097-012-9285-8. [Epub ahead of print].

Klein, S. B., Cosmides, L., Tooby, J., and Chance, S. (2002a). Decisions and the evolution of memory: multiple systems, multiple functions. *Psychol. Rev.* 109, 306–329.

Klein, S. B., Loftus, J., and Kihlstrom, J. F. (2002b). Memory and temporal experience: the effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. *Soc. Cogn.* 20, 353–379.

Klein, S. B., Rozendale, K., and Cosmides, L. (2002c). A social-cognitive neuroscience analysis of the self. *Soc. Cogn.* 20, 105–135.

Klein, S. B., and Gangi, C. E. (2010). The multiplicity of self: Neuropsychological evidence and its implications for the self as a construct in psychological research. *Ann. N.Y. Acad. Sci.* 1191, 1–15.

Klein, S. B., German, T. P., Cosmides, L., and Gabriel, R. (2004). A theory of autobiographical memory: necessary components and disorders resulting from their loss. *Soc. Cogn.* 22, 460–490.

Klein, S. B., Robertson, T. E., and Delton, A. W. (2010). Facing the future: memory as an evolved system for planning future acts. *Mem. Cogn.* 38, 13–22.

Klein, S. B., and Lax, M. L. (2010). The unanticipated resilience of trait self-knowledge in the face of neural damage. *Memory* 18, 918–948.

Klein, S. B., and Nichols, S. (2012). Memory and the sense of personal identity. *Mind* 121, 677–702.

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.* 11, 724–744.

Ladyman, J. (2002). *Understanding Philosophy of Science*. New York, NY: Routledge.

Lane, T. (2012). Toward an explanatory framework for mental ownership. *Phenomenol. Cogn. Sci.* 11, 251–286.

Levy, D. A., Bayley, P. J., and Squire, L. R. (2004). The anatomy of semantic knowledge: medial vs. lateral temporal lobe. *Proc. Natl. Acad. Sci.U.S.A.* 101, 6710–6715.

Lipton, P. (1991). *Inference to the Best Explanation, 2nd Edn.* New York, NY: Routledge.

Locke, D. (1968). *Myself and Others.* Oxford: Clarendon Press.

Markowitsch, H. J. (2003). "Autonoetic consciousness," in *The Self in Neuroscience and Psychiatry,* eds T. Kircher and A. David (Cambridge: Cambridge University Press), 180–196.

Markowitsch, H. J., and Staniliou, A. (2011). Memory, autonoetic consciousness, and the self. *Conscious. Cogn.* 20, 16–39.

Martinelli, P., Sperduti, M., and Piolino, P. (2012). Neural substrates of the self-memory system: new insights from a meta-analysis. *Hum. Brain Mapp.* doi: 10.1002/hbm.22008. [Epub ahead of print].

McCarthy, R. A., and Warrington, E. K. (1992). Actors but not scripts: the dissociation of people and events in retrograde amnesia. *Neuropsychologia* 30, 633–644.

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., and Rosenbaum, R. S. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr. Opin. Neurobiol.* 16, 179–190.

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., et al. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J. Anat.* 207, 35–66.

Nadel., L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* 7, 217–227.

Nagel, T. (1974). What is it like to be a bat? *Philos. Rev.* 83, 435–450.

Naya, Y., and Suzuki, W. A. (2011). Integrating 'what' and 'when' across the primate medial temporal lobe. *Science* 5, 773–776.

Newell, A. (1973). "You can't play 20 questions with nature and win: projective components on the papers of this symposium," in *Visual Information Processing,* ed W. G. Chase (New York, NY: Academic Press), 283–308.

Northoff, G. (2000). Are "Q-Memories" empirically realistic? A neurophilosophical approach. *Philos. Psychol.* 13, 191–211.

Nyberg, L., Cabeza, R., and Tulving, E. (1996). PET studies of encoding and retrieval: the HERA model. *Psychon. Bull. Rev.* 3, 135–148.

Nyberg, L., and Tulving, E. (1998). Functional brain imaging of episodic and semantic memory with positron emission tomography. *J. Mol. Med.* 76, 48–53.

Parkin, A. J. (1997). *Memory and Amnesia, 2nd Edn.* Oxford: Basil Blackwell.

Perner, J., and Ruffman, T. (1994). Episodic memory and autonoetic consciousness: developmental evidence and a theory of childhood amnesia. *J. Exp. Child Psychol.* 59, 516–548.

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalavee, C., De La Sayette, V., et al. (2003). Autobiographical memory and autonoteic consciousness: triple dissociation in neurogenerative diseases. *Brain* 126, 2203–2219.

Polanyi, M. (1967). *The Tacit Dimension*. Garden City, NY: Anchor Books.

Rasmussen, K. W., and Bernsten, D. (2012). Autobiographical memory and episodic future thinking after moderate to severe traumatic brain injury. *J. Neuropsychol.* doi: 10.1111/jnp.12003. [Epub ahead of print].

Reid, T. (1813/1969). *Essays on the Intellectual Powers of Man.* Cambridge, MA: MIT Press.

Renoult, L., Davidson, P. S. R., Palombo, D. J., Moscovitch, M., and Levine, B. (in press). Personal semantics: at the crossroads of semantic and episodic memory. *Trends Cogn. Sci.*

Robertson, L. C., Knight, R. T., Rafal, R., and Shimamura, A. P. (1993). Cognitive neuropsychology is more than single case studies. *J. Exp. Psychol. Learn. Mem. Cogn.* 19, 710–717.

Rosenbaum, R. S., Murphy, K. J., and Rich, J. B. (2012). The amnesias. *Wiley Interdiscip. Rev. Cogn. Sci.* 3, 47–63.

Russell, B. (1912/1999). *The Problems of Philosophy.* Mineola, NY: Dover Publications.

Russell, B. (1921). *The Analysis of Mind*. London: George Allen and Unwin Ltd.

Ryan, L., Cox, C., Hayes, S. M., and Nadel, L. (2008). Hippocampal activation during episodic and semantic memory retrieval: comparing category production and cued recall. *Neuropsychologia* 46, 2109–2121.

Sass, L. A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr. Bull.* 29, 427–444.

Schacter, D. L. (1995). *Memory Distortion*. Cambridge, MA: Harvard University Press.

Schacter, D. L., and Tulving, E. (eds.). (1994). *Memory Systems*. Cambridge, MA: MIT Press.

Schwindt, G., and Black, S. E. (2009). Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative analysis. *Neuroimage* 45, 181–190.

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21.

Shallice, T. (1988). *From Neuropsychology to Mental Structure*. Cambridge: Cambridge University Press.

Smith, C. N., and Squire, L. R. (2009). Medial temporal lobe activity during retrieval of semantic memory is related to the age of the memory. *J. Neurosci.* 29, 930–938.

Sokol, S. M., McCloskey, M., Cohen, N. J., and Aliminosa, D. (1991). Cognitive representations and processes in arithmetic: inferences from the performance of brain-damaged subjects. *J. Exp. Psychol. Learn. Mem. Cogn.* 17, 355–376.

Squire, L. R. (1987). *Memory and Brain*. New York, NY: Oxford University Press.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol. Learn. Mem.* 82, 171–177.

Squire, L. R., and Bayley, P. J. (2007). The neuroscience of remote memory. *Curr. Opin. Neurobiol.* 17, 185–196.

Stephens, G. L., and Graham, G. (2000). *When Self-Consciousness Breaks: Alien Voices and Inserted Thoughts*. Cambridge, MA: MIT Press.

Stuss, D. T., and Guzman, D. A. (1988). Severe remote memory loss with minimal anterograde amnesia: a clincial note. *Brain Cogn.* 8, 21–30.

Suddendorf, T., and Corballis, M. C. (1997). Mental time travel and the evolution of the human mind. *Genet. Soc. Gen. Psychol. Monogr.* 123, 133–167.

Suddendorf, T., and Corballis, M. C. (2007). The evolution of foresight:

what is mental time travel, and is it unique to humans? *Behav. Brain Sci.* 30, 299–313.

Svoboda, E., McKinnon, M. C., and Levince, B. L. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208.

Szpunar, K. K. (2010). Episodic future thought: an emerging concept. *Perspect. Psychol. Sci.* 5, 142–162.

Szpunar, K. K. (2011). On subjective time. *Cortex* 47, 409–411.

Szpunar, K. K., and Tulving, E. (2011). "Varieties of future experience," in *Predictions and the Brain: Using Our Past to Generate a Future,* ed M. Bar (New York, NY: Oxford University Press), 3–12.

Talland, G. A. (1964). Self-reference: a neglected component in remembering. *Am. Psychol.* 19, 351–353.

Trusted, J. (1987). *Inquiry and Understanding: An Introduction to Explanation on the Physical and Human Science*s. Atlantic Highlands, NJ: Humanities Press.

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory,* eds E. Tulving and W. Donaldson (New York, NY: Academic Press), 381–403.

Tulving, E. (1983). *Elements of Episodic Memory*. New York, NY: Oxford University Press.

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12.

Tulving, E. (1993). "Self-knowledge of an amnesic individual is represented abstractly," in *Advances in Social Cognition*, *Vol. 5,* eds T. K. Srull and R. S. Wyer (Hillsdale, NJ: Erlbaum), 147–156.

Tulving, E. (2002). Episodic memory: from mind to brain. *Ann. Rev. Psychol.* 53, 1–25.

Tulving, E., Schacter, D. L., McLachlan, D. R., and Moscovitch, M. (1988). Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. *Brain Cogn.* 8, 3–20.

Tulving, E., and Szpunar, K. K. (2012). "Does the future exist?" in *Mind and the Frontal Lobes: Cognition, Behavior, and Brain Imaging,* eds B. Levince and F. I. M. Craik (New York, NY: Oxford University Press), 248–263.

Uttal, W. R. (2001). *The New Phrenology*. Cambridge, MA: MIT Press.

Uttal, W. R. (2009). *Distributed Neural Systems*. Cormwall-on-Hudson, NY: Sloan Publishing.

Wagner, A. D., Shannon, B. J., Kahn, I., and Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn. Sci.* 9, 445–453.

Warnock, M. (1987). *Memory*. Boston, MA: Faber and Faber.

Wheeler, M. A. (2000). "Varieties of memory and consciousness in the developing child," in *Memory, Consciousness and the Brain: The Tallin Conference,* ed E. Tulving (Philadelphia, PA: Psychology Press), 188–199.

Wheeler, M. A. (2005). "Theories of Memory and Consciousness," in *The Oxford Handbook of Memory,* eds E. Tulving and F. I. M. Craik (Oxford: Oxford University Press), 597–608.

Wheeler, M. A., Stuss, D. T., and Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychol. Bull.* 121, 331–354.

Williams, G. C. (1966). *Adaptation and Natural Selection: A Critique of Some Current Evolutionary Thought*. Princeton, NJ: Princeton University Press.

Wixted, J. T., and Mickes, L. (2010). A continuous dual-process model of remember/know Judgments. *Psychol. Rev.* 117, 1025–1054.

Zahavi, D. (2005). *Subjectivity and Selfhood: Investigating the First-Person Perspective*. Cambridge, MA: The MIT Press.

Zahn, R., Talazko, J., and Ebert, D. (2007). Loss of sense of self-ownership for perceptions of objects in a case of right inferior temporal, parieto-occipital and precentral hypometabolism. *Psychopathology* 41, 397–402.

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Associative learning beyond the medial temporal lobe: many actors on the memory stage

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Decades of research have established a model that includes the medial temporal lobe, and particularly the hippocampus, as a critical node for episodic memory. Neuroimaging and clinical studies have shown the involvement of additional cortical and subcortical regions. Among these areas, the thalamus, the retrosplenial cortex, and the prefrontal cortices have been consistently related to episodic memory performance. This article provides evidences that these areas are in different forms and degrees critical for human memory function rather than playing only an ancillary role. First we briefly summarize the functional architecture of the medial temporal lobe with respect to recognition memory and recall. We then focus on the clinical and neuroimaging evidence available on thalamo-prefrontal and thalamo-retrosplenial networks. The role of these networks in episodic memory has been considered secondary, partly because disruption of these areas does not always lead to severe impairments; to account for this evidence, we discuss methodological issues related to the investigation of these regions. We propose that these networks contribute differently to recognition memory and recall, and also that the memory stage of their contribution shows specificity to encoding or retrieval in recall tasks. We note that the same mechanisms may be in force when humans perform non-episodic tasks, e.g., semantic retrieval and mental time travel. Functional disturbance of these networks is related to cognitive impairments not only in neurological disorders, but also in psychiatric medical conditions, such as schizophrenia. Finally we discuss possible mechanisms for the contribution of these areas to memory, including regulation of oscillatory rhythms and long-term potentiation. We conclude that integrity of the thalamo-frontal and the thalamo-retrosplenial networks is necessary for the manifold features of episodic memory.

Keywords: recognition memory, recollection, familiarity, recall, thalamus, retrosplenial cortex, prefrontal cortex, schizophrenia

> The only proof of there being retention is that recall actually takes place
>
> (James, 1890).

Memory is a fascinating puzzle for neuroscientists: at first glance it seems straightforward to grasp the unity of this cognitive skill and its adaptive meaning; one is prompted to search for the storage room in the brain, like it happened in the beginning of memory research. Today there is consensus that many memory systems rely on dissociable neural substrates (Squire and Kandel, 2000). Within cognitive neuroscience, different research fields kept searching for a main character of the "memory play." The best candidate for episodic memory, as defined by Tulving (1987, 2002) and Tulving and Markowitsch (1997, 1998), has been the hippocampus (HC[1]; Scoville and Milner, 1957).

Destruction of the HC is sufficient to wipe out novel episodic learning in humans and non-human primates (Mishkin, 1982; Zola-Morgan et al., 1982; reviewed by Aggleton and Brown, 1999). A less straightforward question is whether the loss of hippocampal function is necessary for episodic memory impairments. Damage to other regions, including the cortices of the parahippocampal gyrus, the prefrontal cortex (PFC), the thalamus, and the retrosplenial and posterior cingulate cortex (RSC), may also result in memory deficits (reviewed by Aggleton and Brown, 1999; Kopelman, 2002; Van der Werf et al., 2003a; Eichenbaum et al., 2007; Mitchell and Johnson, 2009; Vann et al., 2009a; Brown et al., 2010). All of these regions presumably perform operations that differ at least to some extent, so what we call "episodic memory" is the result of a number of sub-functions underlay by many brain regions.

A logical consequence is that damage to different brain areas leads to qualitatively different episodic memory impairments; this argument also applies to brain activations detected by means of neuroimaging techniques, which will overlap to a large extent, but not completely, depending on subtle task differences. One strategy to attack this complexity is to "average" the evidence and single out

[1]For the sake of simplicity the term "hippocampus," abbreviated with HC, refers throughout the article to the hippocampal formation, including the dentate gyrus, CA fields, subiculum, presubiculum, and parasubiculum. Aggleton (2012) goes more in detail with respect to the connectivity of HC subregions and should be consulted for further reference.

brain regions which regularly contribute to episodic memory. This way of proceeding is robust with respect to the inferences drawn, e.g., we can predict that surgical ablation of the HC will instantiate amnesia. However, this procedure is insufficient to study more fine-grained mechanisms underlying episodic memory, for example as a function of stimulus material or memory stage. This article reviews evidence on the involvement of other brain structures, aside from the HC, in what is the hallmark of HC-dependent memory: recall.

We will discuss clinical and neuroimaging literature about brain networks supporting different aspects of recall, particularly a thalamic-PFC and a thalamic-RSC network. A main tenet of this work is that interpretation of the results strictly depends on the tasks used to assess memory function. We will therefore argue that empirical work needs to study recall directly and to assess the neurophysiological correlates of recall subprocesses, in order to identify the mechanisms by which different brain regions contribute to recall. Damage to the thalamo-PFC and to the thalamo-RSC networks also impairs other cognitive functions beyond episodic memory, and hypotheses on the mechanisms of contribution of these networks to cognition are discussed in the final part of the review.

THE MAIN ACTOR – A BRIEF REAPPRAISAL ON THE ROLE OF THE MEDIAL TEMPORAL LOBE IN RECOGNITION MEMORY AND RECALL

Since Mandler's (1980) proposal to distinguish a form of recognition accompanied by retrieval of contextual and associative information (recollection) and one more implicit-like, simply consisting of the feeling that something is "old" or "new" (familiarity), the distinction between familiarity and recollection has been investigated widely in cognitive neuroscience. Increasing evidence has emerged in recent years supporting this "dual process model" of recognition memory (Yonelinas, 2002; Eichenbaum et al., 2007; Suchan et al., 2008; Ranganath, 2010; Voss and Paller, 2010). The dual process model assumes that the two processes are qualitatively different. Familiarity is graded and not well suited for associative memory; recollection accomplishes lively and detailed retrieval and is thought to be a threshold process. The main alternative view, the "single process account," assumes a quantitative difference between recollection and familiarity, i.e., stronger memory traces elicit a feeling of recollection (Squire et al., 2007; Slotnick, 2013). Proponents of this view acknowledge that different behavioral outcomes indicate different neural processing within the MTL (Wixted et al., 2010). They stress, however, that tests commonly used introduce confounds in the form of different strength of the memory trace. In general, the techniques used to separately assess recollection and familiarity are debated; for a more complete picture of this controversy it is best to consult more focused reviews (Eichenbaum et al., 2007; Squire et al., 2007; Aggleton et al., 2010; Brown et al., 2010, 2012; Montaldi and Mayes, 2010; Wixted et al., 2010; Rugg et al., 2012; Slotnick, 2013).

The MTL includes the HC and the parahippocampal cortices. The neocortical areas that send inputs into and receive outputs from the MTL include all higher order "association" areas and no primary sensory (except for the olfactory) or motor cortices. This connectivity pattern is illustrated in **Figure 1**. The HC is on top of this information flow (Lavenex and Amaral, 2000; Witter et al.,

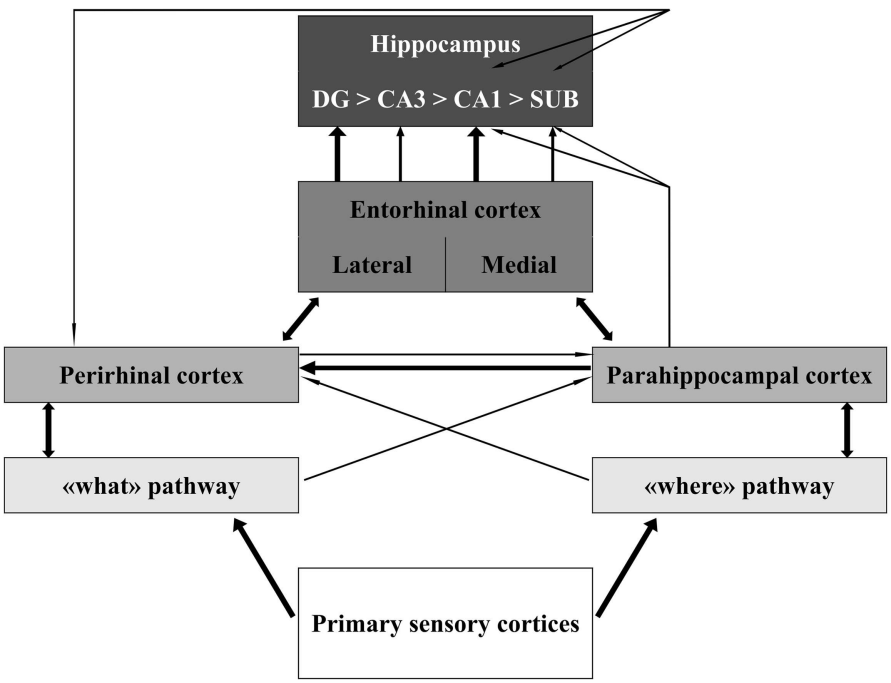


FIGURE 1 | Schematic representation of the organization of the medial temporal lobe in information processing. The thickness of the lines represents the weight of the connections. Notice that sensory information is only partly integrated at the level of the perirhinal, parahippocampal, and entorhinal cortices. Information about different aspects of the sensory stimulus converges in the hippocampus through largely segregated pathways. Modified from Aggleton (2012). Abbreviations: DG, dentate gyrus; CA, cornus ammonis; SUB, subiculum.

2000; Eichenbaum and Lipton, 2008). The outputs of hippocampal processing are directed back down this information path in reversed order.

It is debated whether the distinct processes subserved by the HC and the parahippocampal cortices correspond to recollection and familiarity (Yonelinas et al., 1998; Holdstock et al., 2002, 2005; Mayes et al., 2002; Yonelinas, 2002; Davachi et al., 2003; Bastin et al., 2004; Ranganath et al., 2004; Aggleton et al., 2005; Uncapher and Rugg, 2005a,b; Montaldi et al., 2006; Uncapher et al., 2006). There is agreement, however, that associative memory encoding tasks recruit the HC, relative to tasks without requirement (or success) of associative encoding (Henke et al., 1997, 1999; Sperling et al., 2003; Achim and Lepage, 2005; Chua et al., 2007). The neural substrates of recognition memory also depend on more subtle differences related to stimuli presentation (Henderson et al., 2003; Cipolotti et al., 2006; Bird et al., 2007; Peters et al., 2007a,b; Awipi and Davachi, 2008). Of interest to the empirical setting of novel investigations, there is consensus that recall and recognition are dissociable cognitive skills, and that the HC is necessary for recall, but likely insufficient. Yonelinas et al. (2010), for instance, highlighted the role of the PFC in recognition memory, concluding that the extant evidence favors a prefrontal contribution to recollection, in particular during encoding.

Thus, the constituents of the MTL play different roles in recognition memory and recall, with a major role of the HC in recall. The contribution of other areas of the MTL to recognition memory is intensely debated. Beyond the MTL, there is evidence on the involvement of other brain areas in recall. This will be the subject of Section "A Crowded Stage – Evidence for Other Recognition and Recall Networks."

INTRICATED PLOTS – HOW TO ASSESS THE CONTRIBUTION OF THALAMO-CORTICAL NETWORKS TO MEMORY

Since this review focuses on clinical and neuroimaging evidence, we will briefly discuss the impact of testing procedures on results derived by these techniques.

Recognition memory tasks fall into two major categories: subjective and objective (Eichenbaum et al., 2007). Subjective tasks rely on self-assessment of memory traces, and include for instance the remember/know paradigm (Tulving, 1987) and the receiving operating curves based on confidence levels (Yonelinas, 2002). Objective paradigms, instead, test directly for memory of associations related to the recognition cue; source memory and recall tests are examples of this kind of experimental procedure.

In remember/know paradigms subjects are instructed to assess whether their memory is more based on conscious associations or on "feelings" of familiarity, entailing the sensation that one "knows" an item but does not "remember" anything about it. These paradigms have been criticized because they may rather tap subjective awareness of one's memory than "true" features of the memory trace (Gardiner, 1988; Newell and Dunn, 2008; Geraci et al., 2009; McCabe and Geraci, 2009). Moreover, memory strength might confound remember/know results (Slotnick, 2013).

Receiving operating curves, on the other hand, cannot discriminate between "recollected" and "recognized" stimuli, but provide a global estimation of familiarity and recollection in one condition, individual, or group. The estimates are based on the notion that recollection is a threshold process (Yonelinas et al., 2010), an assumption that did not fail to trigger criticism (Wixted et al., 2010; Slotnick, 2013), although recent fMRI evidence appears to support it (Pustina et al., 2012). On the other hand, the idea that lower confidence involves greater familiarity is still prone to the alternative interpretation that recollection simply reflects greater memory strength (Wixted, 2007).

Montaldi et al. (2006) and Kafkas and Montaldi (2012) developed a subjective task that, like Remember/Know, entails training subjects to distinguish recollection from familiarity. Participants focus on familiarity and assess their confidence (from one to three), while recollection should be avoided. If a participant detects that he/she has been using recollection, he/she reports this. This task effectively matches memory strength, with the caveat that subjects are focusing on familiarity: in objective tasks they are usually actively engaged in recall. This novel subjective task appears to be a promising tool to study familiarity free of the "memory strength" confound. Results obtained on "recollection" trials by using this task, however, share the general limitations of subjective tasks and introduce the additional feature that recollection is undesired. Participants' orientation at encoding and retrieval may be different from what is typical in objective tasks.

Objective paradigms are more powerful than subjective paradigms in indicating recollection. In particular, objective paradigms allow trial-by-trial discrimination of recollection by asking subjects to report features associated with the recognition cue, which may be perceptual (e.g., color; Cycowicz et al., 2001), contextual (e.g., place where the cue was previously shown; Cansino et al., 2002), semantic (e.g., match or mismatch with the category of other items; Pergola et al., 2013b), and episodic (e.g., decision taken during previous exposure or imagination of the items; Vilberg and Rugg, 2012). There is general agreement that, when memory strength and confidence are equated, recollection is more likely to be involved in recognition memory followed by recall, as compared to familiarity (Brown et al., 2010; Wixted et al., 2010).

Nevertheless, objective paradigms present a certain degree of variability, and subtle details can change the pattern of activations in a neuroimaging study, as well as the pattern of deficits displayed by clinical samples. For example, it has been shown that some forced choice tasks also entail neural correlates typical of familiarity (Quamme et al., 2007; Diana et al., 2008). Mayes et al. (2007) proposed that this might happen because of lower-level relational operations performed in the parahippocampal and perirhinal cortices. Items belonging to the same context (e.g., steer and brakes in a car) might be encoded already at the level of the perirhinal cortex: overlearned associations require less integration. This argument extends to material learned through "unitized" representation (e.g., the word association sun-set compared to sun-toy). Moreover, remembering the information associated with a recognition cue when choosing between two and three possibilities is prone to guessing influence. Recall tasks which require retrieval of a unique association, instead, are robust with respect to guesses and to familiarity (Montaldi and Mayes, 2010), a strategy recently used in both clinical and neuroimaging setting (Pergola et al., 2012, 2013b,d). The trials in which correct recall occurs are most likely recollection trials, although the converse is not true: it is possible that a participant recognizes the cue based on recall, but

not on recall of the information tested, e.g., an associated picture or context (non-criterial recollection: see Yonelinas et al., 2010).

In our opinion, investigations of the recollection/familiarity dichotomy are made difficult by the pragmatic definitions of recollection and familiarity. Both are thought to support recognition, and additionally recollection is thought to support recall. Hence evidence of recall is commonly used to infer recollection; lack of recall is used to infer familiarity (see for example Slotnick, 2013). However, in order to show the involvement of a brain structure in familiarity processing, it is necessary to find exclusive correlates of familiarity – something that recollection *cannot* support. It is our impression that consensus on such specialized features of familiarity has not yet been reached. Putative correlates of familiarity that have been disputed include reaction times, responses given under time pressure, differential modulation of responses induced by perceptual manipulation, and electrophysiological components (Eichenbaum et al., 2007; Squire et al., 2007; Brown et al., 2010, 2012; Montaldi and Mayes, 2010; Wixted et al., 2010; Paller et al., 2012; Rugg et al., 2012). The paradigms that seem most successful in detecting familiarity are subjective tasks (Yonelinas, 2002; Montaldi et al., 2006), within the limitations discussed. Hypotheses about the involvement of select brain structures in familiarity appear empirically ill-posed, if they must rely on lack of evidence of recollection.

Following this framework, in the following we will differentiate *recall* (i.e., recognition memory followed by recall of contextual or associative details) and *recognition without recall* (i.e., correct judgment of previous occurrence not followed by successful retrieval of contextual and associative information). These behavioral outcomes are easier to probe empirically than the putative underlying processes (recollection and familiarity). It is important for the following of the article to keep in mind this distinction between behavior and underlying processes.

A CROWDED STAGE – EVIDENCE FOR OTHER RECOGNITION AND RECALL NETWORKS

The earliest observations on non-hippocampal based amnesia relate to the "Wernicke–Korsakoff syndrome," a degenerative disease caused by depletion of thiamine (often secondary to alcohol abuse; for reviews see Kopelman, 2002; Kopelman et al., 2009). Amnesic symptoms in Korsakoff patients have been related to damage in the mammillary bodies and the anterior nuclei of the thalamus (abbreviated in the following as AT; Victor et al., 1989; Harding et al., 2000). Another clinical condition leading to amnesia is thalamic stroke (reviewed by Schmahmann, 2003; Carlesimo et al., 2011). Behavioral symptoms include anterograde amnesia, executive deficits, and rarely retrograde memory loss. Implicit memory is mostly preserved, much like in hippocampal amnesia (Daum and Ackermann, 1994; but see Exner et al., 2001).

Aggleton and Brown (1999) challenged the distinction between medial temporal and subcortical amnesias by proposing that the AT are functionally linked to the HC (i.e., critical for recollection), while the mediodorsal nucleus (MD) contributes more to familiarity based on its connections to the perirhinal cortex. This model has been recently revised (see Aggleton et al., 2011, for an update). We will now evaluate the extant evidence on the role of the MD and the AT in recognition memory in the framework of the thalamo-PFC and the thalamo-RSC networks.

THE THALAMO-PREFRONTAL NETWORK

The conspicuous evidence delineating the anatomical basis of the thalamic-PFC network has already been discussed elsewhere (Taber et al., 2004; Byne et al., 2009; Klein et al., 2010; Barbas et al., 2012). **Figure 2** illustrates the main patterns of anatomical connection of this network.

At least three important circuits involved in episodic memory relate the thalamus and the PFC. The first is the reciprocal MD-PFC connection, which shows corresponding thalamic mediolateral and prefrontal ventromedial-dorsolateral topographical gradients (Russchen et al., 1987; Barbas et al., 1991; Ray and Price, 1993). In other words, the MD-PFC connectivity is not homogeneous within the nucleus. In humans, the MD[2] is comprised of a magnocellular portion (MDmc), covering the medial third of it, and a parvocellular portion (MDpc), larger and lateral to the MDmc. The connectivity patterns of the MDmc and the MDpc differ (for discussion see Barbas et al., 2012; Pergola et al., 2012; Mitchell and Chakraborty, 2013). The MDmc is reciprocally connected to the ventromedial PFC and also receives afferents from the MTL (Aggleton, 2012). The MDpc, instead, is reciprocally connected to the dorsolateral PFC (DLPFC) and this is its major source of input, although it receives further input from other prefrontal areas (Mitchell and Chakraborty, 2013). There is no evidence of input from the MTL to the MDpc (Mitchell and Chakraborty, 2013). Byne et al. (2009) observed that, similar to the MDmc, also the medial pulvinar is connected to the PFC as well as with temporal and parietal cortices, and may be involved in declarative memory (see also Nadeau and Crosson, 1997). This suggestion has been supported by more recent neuroimaging findings on pulvinar activations during associative memory encoding (Pergola et al., 2013b).

The second pathway includes the diffuse projections from the intralaminar nuclei (ILN)[3] to the PFC. While the ILN send specific projections to the basal ganglia (Preuss and Goldman-Rakic, 1987; Barbas et al., 1991; Sadikot et al., 1992), projections to the PFC are more sparse and widespread. The functional role of these connections is unclear. The ILN are considered part of a cerebellar-striato-frontal network that has been proposed to be essential for language production and control (Nadeau and Crosson, 1997). It has also been proposed that the activity of these nuclei may rapidly recruit large cortical portions and entrain synchronization of cortical activity (reviewed by Jones, 2007), hence contributing to allocate attentional resources (Van der Werf et al., 2002).

A third pathway, proposed to especially contribute to attention control, includes the reticular thalamic nucleus (RTN), the main source of GABAergic input to the thalamus. The thalamo-cortical cells of the AT, MD, and other nuclei are mostly glutamatergic and excite cortical neurons; local GABAergic interneurons,

[2]Throughout the review we will endorse the viewpoint expressed by Jones (2007) that other partitions of the MD (densocellular, paralamellar, or multiformis) rather belong to the centrolateral nucleus, which is considered part of the ILN.

[3]As specified in the previous footnote, this group of thalamic nuclei includes the densocellular and paralamellar (or multiformis) partition of the MD in the current review.

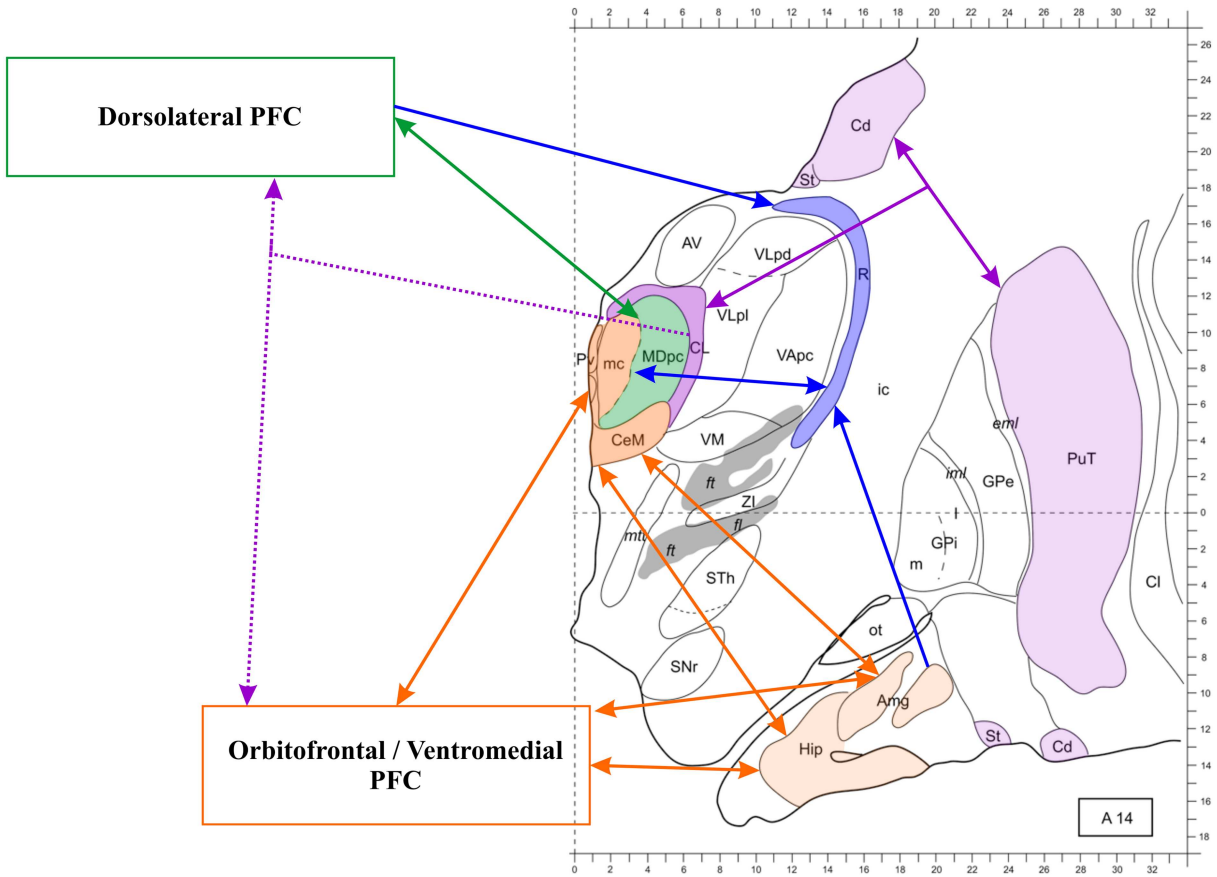


FIGURE 2 | The thalamo-prefrontal cortical network. Transversal section 14 mm anterior to the posterior commissura. The thalamus and the prefrontal cortex (PFC) are connected through partly independent pathways. Dotted lines represent widespread projections. Notice the triangular connections involving the medial temporal lobe, the midline thalamus and the orbitofrontal, and ventromedial cortex. The mediodorsal nucleus (MD) is involved in multiple pathways, also including the reticular nucleus (R), which receives projections from the PFC and the amygdala as well as reciprocal connections to the MD (both subunits). The MDmc, which is represented in the same color as the midline nuclei because they present functional commonalities, is not connected to the hippocampus, but it receives amygdalar projections and is reciprocally connected to the orbitofrontal and ventromedial PFC. The intralaminar nuclei (only the centrolateral nucleus (CL) is represented in this section) are part of the thalamo-striato-frontal network (striato-frontal connections are not represented). Modified from Morel (2007). Abbreviations: Amg, amygdala; AV, anteroventral nucleus; Cd, caudate nucleus; Cl, claustrum; eml, external medullary lamina; ft, fasciculus thalamicus; ic, internal capsula; iml, internal medullary lamina; GPe, globus pallidum, pars externa; GPi, globus pallidum, pars interna; Hip, hippocampus; MDpc, parvocellular MD; mc, magnocellular MD; mtt, mammillothalamic tract; ot, olfactory tubercle; PuT, putamen; Pv, paraventricular nucleus; SNr, substantia nigra, pars reticulate; St, striatum; STh, subthalamic nucleus; VApc, ventral anterior nucleus, parvocellular portion; VLpd, ventrolateral nucleus, posterior dorsal subunit; VLpl, posterior lateral subunit; VM, ventromedial nucleus; Zl, zona incerta.

however, constitute up to 25–30% of cells, a peculiarity of the primate thalamus, compared to the rodent thalamus (reviewed by Jones, 2007). Beyond this "intrinsic" inhibition, thalamic nuclei are regulated by the RTN, which receives collaterals from both thalamo-cortical and cortico-thalamic fibers, but only inhibits thalamic cells (Avanzini et al., 1996). Therefore this nucleus is in the place to switch between patterns of thalamic electrophysiological activity, by selectively inhibiting the thalamo-cortical projections (Crick, 1984). Notably, the left and right RTN are connected directly, unlike most nuclei of the dorsal thalamus. The topographical order of the connections between the RTN and the nuclei of the dorsal thalamus forms "sectors" of the RTN that selectively control specific circuits and functions, thus affecting specific cortical areas (Barbas et al., 2012). On the other hand, the activity of an RTN subregion can quickly recruit the whole nucleus, and thereby the whole thalamo-cortical network, through gap junctions (Wang and Rinzel, 1993). Intriguingly, the MD interacts in a specific way with the RTN. All other nuclei project to a specific sector of the RTN, whereas the MD projects to all RTN subregions (Barbas et al., 2012). The same holds for the PFC, which regulates RTN activity as a whole (Zikopoulos and Barbas, 2006). This anatomical evidence suggests that the MD-PFC-RTN circuitry is critical for allocating cognitive resources and that the MD-PFC interactions are able to effectively modulate the activity in other thalamic areas through the interaction with the RTN. In sum, anatomical evidence differentiates three integrated components of the thalamo-PFC network: the MD-PFC connections, further composed of two pathways (magnocellular and parvocellular)

which project to distinct cortical areas; the ILN-PFC connections; and the RTN-PFC connection, which also interacts with the MD.

Lesion studies in animals highlighted the importance of this MD-PFC system for episodic memory (see Mitchell and Chakraborty, 2013 for review). However, it has been suggested that deficits found in rewarded recognition tasks may reflect the effects of MD damage on aspects of task performance other than recognition, particularly on reward association learning (Corbit et al., 2003; Cross et al., 2012; see Baxter, 2013 for a discussion based on evidence from non-human primates). There might be differences between rodents and primates as concerns the role of the MD-PFC network in recognition memory, reflecting a greater influence of PFC-dependant processing in object recognition in primates (Aggleton et al., 2011; Cross et al., 2012). This notion can help reconcile seemingly contrasting findings in animals and humans. The MD nuclei of rodents and primates differ in the relative dimensions of their subunits, in the expression of intrinsic GABAergic neurons (reviewed by Jones, 2007), in the connectivity to the RTN (Zikopoulos and Barbas, 2012), in the expression of dopaminergic receptors (Garcia-Cabezas et al., 2007, 2009) and of transcripts related to dopaminergic transmission (Hurd and Fagergren, 2000). So many differences entangle inferences on the functions of the human thalamo-PFC network based on work with rodents.

The evidence available based on studies with non-human primates confirms the role of this network in learning and memory, especially with respect to an involvement of the MDmc in encoding (reviewed by Baxter, 2013). Even though the concerns about mixed influences of episodic memory and reward processing still apply, work with animal models highlights multiple interactions between the thalamus and the PFC, with the MD being a key hub of the network.

Clinical evidence

Patients with frontal lobe lesions are impaired in recognition and recall, with disproportionate impairment on the latter (Shimamura, 1995; Wheeler et al., 1995). These patients have difficulties with strategic aspects of recall, i.e., effectively generating and using cues to build/retrieve memory traces. The PFC is ubiquitously activated in recognition memory fMRI experiments (Cansino et al., 2002; Dobbins and Wagner, 2005; see Mitchell and Johnson, 2009 for a review), yet its exact contribution is far from clear. In event-related potentials (ERP) studies, frontal activity is found during episodic memory encoding (Neufang et al., 2006; Blumenfeld and Ranganath, 2007; Kim et al., 2009; Pergola et al., 2013d), as well as retrieval (Allan and Rugg, 1998; Duzel et al., 1999; Ranganath et al., 2000; Badgaiyan et al., 2002; Dobbins et al., 2002; Rugg and Curran, 2007; Pergola et al., 2013d). Most likely, the pattern of activations found in recognition memory studies at frontal sites actually depends on the activity of several PFC subregions processing novelty detection, relational encoding, maintenance, weighing, and selection of concurrent responses (Thompson-Schill et al., 1997; Dobbins and Han, 2006; Blumenfeld and Ranganath, 2007; Burgess et al., 2007; Bergstrom et al., 2013). For example, the ventrolateral PFC seems involved in memory formation irrespective of its associative nature (Blumenfeld and Ranganath, 2007; Mitchell and Johnson, 2009), while the DLPFC specifically contributes to successful associative encoding (Dolan and Fletcher, 1997; Staresina and Davachi, 2006; Murray and Ranganath, 2007; Mitchell and Johnson, 2009; Blumenfeld et al., 2011; Huijbers et al., 2013).

As regards the thalamus, deficits of recall and associative memory have been documented following ischemic lesion in the territory of the MD (Zoppelt et al., 2003; Edelstyn et al., 2006, 2012a; Soei et al., 2008), although those studies could not rule out a role of damage to the mammillothalamic tract (MTT) in the deficit pattern (discussed by Carlesimo et al., 2011; the MTT is considered part of the thalamo-RSC network). We performed a systematic review[4] of all case reports of thalamic stroke *with damage in the territory of the MD and without apparent damage in the territory of the AT and the MTT*. Only reports including neuropsychological assessment of memory skills were included. Results are shown in **Table 1**.

We considered 17 studies, for a total of 44 cases. A first look at **Table 1** reveals how heterogeneous the cases were with respect to laterality, lesion-test interval, and lesion assessment. The paucity of studies meeting the requirements we set and their heterogeneity aligns with the current lack of agreement on the function of the MD.

This analysis reveals that no single report documents impairments of recognition without recall deficits (**Table 1**, columns VII and VIII), a fact also acknowledged by other researchers (Aggleton et al., 2011; Carlesimo et al., 2011; Mitchell and Chakraborty, 2013). The general pattern of deficits is consistent with the idea that a primary impairment on recall entails a deficit in recognition memory because of disrupted recollection (Pergola et al., 2012).

The picture becomes more complicated when the evidence is evaluated more strictly. In several studies (**Table 2**, gray background) lesion to the MTT or to extrathalamic regions cannot be excluded; in others, pharmacological treatment or history of psychiatric disorders and/or substance abuse limit the clarity of the results. When studies with these potential confounds are excluded, only 13 cases remain (von Cramon et al., 1985; Kritchevsky et al., 1987; Calabrese et al., 1993; Shuren et al., 1997; Van der Werf et al., 2003b; Pergola et al., 2012). Two observations can be made on these studies: first, these most informative reports document less severe deficits; second, it seems that more recent reports found greater impairments compared to the earlier ones. We suggest that more recent studies employed more sensitive and/or extensive testing, changing the framework from the study of "amnesia" to the study of specific memory deficits.

Pergola et al. (2012), for instance, found a decline in recall performance in patients with focal medial thalamic stroke, who were not impaired in recognition without recall. The task involved single-item recognition and cued recall of uniquely paired

[4]Articles were considered based on previous reviews and on the PubMed search: (thalam*[title/abstract]) AND (stroke[title/abstract] OR infarct[title/abstract] OR ischemia[title/abstract] OR ischaemia[title/abstract] OR ischemic[title/abstract]) AND (memory[title/abstract] OR learning[title/abstract] OR recollection[title/abstract] OR recognition[title/abstract] OR familiarity[title/abstract] OR amnesia[title/abstract] OR amnesic[title/abstract]) AND english[language].

Table 1 | Clinical literature on cases with lesion to the mediodorsal thalamic nucleus.

I. Article	II. Laterality	III. Phase of lesion at test	IV. MTT involvement	V. Medial MD lesion	VI. Lateral MD lesion	VII. Recall	VIII. Recognition	IX. Encoding deficits	X. Retrieval deficits	XI. Comments
Speedie and Heilman (1982)	L	Acute, sub-acute	*Perhaps*	Unclear	Unclear	Impaired	NA	–	Apparent deficit only after delay	CT scan suggests that *the MTT could be involved. Psychiatric history*
Winocur et al. (1984)	B	Chronic (<1Y)	*Perhaps*	Yes	Unclear	Impaired	Impaired	Greater deficit after short stimuli presentation	Deficit more evident after delay	CT scan suggests that *the MTT could be involved.* Deficit interpreted as encoding-dependent
von Cramon et al. (1985)[a]	L (P6); B (P5)	Chronic (>1Y)	NO	Minor	Yes, not associated with amnesia	Spared	Spared	–	–	Overlap analysis associated amnesia with MTT damage
Bogousslavsky et al. (1986)	L	Acute	NO	Yes	Yes	Impaired	NA	Short-term memory deficits	–	Post-mortem confirmation. ILN and *extrathalamic damage*
Kritchevsky et al. (1987)	R (P1); B (P2)	Sub-acute	NO	Yes	Only in P2	Spared	Spared	–	–	<15% of MD volume involved
Reilly et al. (1992)	B	Acute, chronic (<1Y)	*Unclear*	Unclear	Unclear	Amnesia (two cases)	NA	Short-term memory deficits	–	Limited neuropsychological examination
Calabrese et al. (1993)	B	Sub-acute	NO	Yes	Minor	Impaired	Impaired	Immediate recall deficits	Deficit more evident after delay	
Shuren et al. (1997)	R	Acute, chronic (<1Y)	NO	Yes	Yes	Spared but source memory deficit	Spared	–		ILN damaged. Source memory for temporal order was selectively impaired
Isaac et al. (1998)	B	Chronic (>1Y)	NO	Yes	Yes	Impaired	Impaired	–	Deficit more evident after delay	*Atrophy of the mammillary bodies*
Fukutake et al. (2002)	L	Sub-acute	NO	Yes	Minor	Spared	NA	–	–	*Test under pharmacological treatment.* Limited neuropsychological examination

(Continued)

Table 1 | Continued

I. Article	II. Laterality	III. Phase of lesion at test	IV. MTT involvement	V. Medial MD lesion	VI. Lateral MD lesion	VII. Recall	VIII. Recognition	IX. Encoding deficits	X. Retrieval deficits	XI. Comments
Van der Werf et al. (2003b)[b]	L	Chronic (>1Y)	NO	NO	Yes	Mildly impaired	Mildly impaired	–	Increased forgetting rate	Impaired visual memory. P13 showed impaired verbal memory and *extrathalamic lesions*
Zoppelt et al. (2003)	L (five cases), R (four cases)	Chronic (mostly >1Y)	*Perhaps*	Two cases, familiarity and recollection deficit	Three cases, recollection deficit	Impaired	Impaired in some cases	Backward span impaired, short-term memory spared	Increased forgetting rate	*Damage to the MTT* was likely in several cases
Tanji et al. (2003)	L	Chronic (<1Y)	NO	Yes	Minor	Impaired	Mildly impaired	Immediate recall deficits	Deficit more evident after delay	*Extrathalamic damage*
Soei et al. (2008)	L (six cases); R (three cases); B (one case)	Chronic (mostly >1Y)	*Perhaps*	Non-associative memory impaired	Milder deficit	Impaired	Impaired in some cases	–	Apparent deficit only after delay	*Damage to the MTT* was likely in several cases
Hampstead and Koffler (2009)	B	Sub-acute	*Perhaps*	Yes	Yes	Impaired	Spared	Immediate recall deficits	Deficit more evident after delay	Profound recall deficit. *History of substance abuse. Extrathalamic damage*
Ioannidis et al. (2012)	B	Chronic (>1Y)	*Unclear*	Yes	Yes	Impaired	NA	Immediate recall deficits	–	Profound recall deficit. Neuroimaging data suggest that *the MTT might have been affected*
Pergola et al. (2012)[c]	L (two cases); R (four cases); B (two cases)	Chronic (>1Y)	NO	Yes	Yes	Impairment proportional to MDpc damage	Impaired in some cases	Immediate recall deficits	Deficit more evident after delay	Relatively mild deficits, with patients mostly between 0 and 3 standard deviations below controls

Only studies in which authors did not find clear evidence of damage to the anterior nuclei (including the laterodorsal nucleus) and to the mammillothalamic tract were included. Shaded rows highlight studies in which confounding factors should be considered when evaluating results. Confounding factors are written in italic font. Acute phase: ≤1 week after lesion onset; sub-acute phase: 1 week < lesion-test interval ≤2 months; chronic phase: >2 months after lesion onset.

B, bilateral lesion; ILN, intralaminar thalamic nuclei; L, left-sided lesion; MD, mediodorsal thalamic nucleus; MTT, mammillothalamic tract; NA, not assessed; P, patient; R, right-sided lesion; Y, year.

[a] *Two cases without AT/MTT damage considered (Patients 5 and 6).*

[b] *Two cases without AT/MTT damage considered (Patients 1 and 13).*

[c] *Eight cases without AT/MTT damage were considered (Patients 2, 3, 5, 6, 7, 8, 9, 16). All patients except for P7, P8, and P9 were free of psychoactive medication.*

associates. Quantitative assessment of the lesions revealed that patients' recall deficits were proportional to damage to the MDpc (but not MDmc/midline or ILN). Even though some of the patients showed evidence of lesion in the MTT, those with no evidence of such damage showed a deficit pattern similar to that of the whole sample. Overlap/subtraction analysis confirmed that in these patients memory deficits were associated to lesion in the MDpc.

This evidence suggests that the MDmc and the MDpc might contribute differently to recognition memory. Zoppelt et al. (2003) proposed that the MDmc could be related to familiarity. Conversely, the recall deficits observed by Pergola et al. (2012) selectively involved the MDpc in recall performance. It can thus be hypothesized that the MDpc is required for recall, while the MDmc is required for recognition without recall. Clinical evidence appears inconclusive in this respect (**Table 1**, columns V and VI), and data from animal studies are problematic for such a proposal (Mitchell and Chakraborty, 2013). Likewise, clinical evidence is of little avail with respect to the contribution of the MD to the encoding or retrieval phase of memory processing (**Table 1**, columns IX and X; Winocur et al., 1984; Mitchell and Chakraborty, 2013).

Neuroimaging evidence

Neuroimaging evidence specifically addressing the role of the thalamus in cognition is sparse (Metzger et al., 2013). To our knowledge, evidence on the differential contribution of the two portions of the MD to episodic memory is limited to a single fMRI study (Pergola et al., 2013b). The study employed a single-item recognition and associative cued recall task and included an anatomical parcellation of the functional clusters activated during task performance. Robust thalamic activation characterized recognition accompanied by recall, compared to recognition not followed by recall, consistent with Achim and Lepage (2005), who found higher thalamic activation during associative than single-item recognition. The MDpc was activated during both encoding and retrieval, similarly to the DLPFC; critically, the MDpc was more activated during recall than during recognition not followed by recall, matching the clinical results and supporting the hypothesis that an MDpc-DLPFC network subserves recall. Activation in the MDmc was only found during retrieval. No thalamic voxel displayed greater activation during recognition without recall compared with recognition followed by recall.

These findings leave unexplained whether the MDmc preferentially supports recognition without recall rather than recall. Perhaps support to this hypothesis comes from two studies performed by Montaldi et al. (2006) and Kafkas and Montaldi (2012), using the task previously described (see Intricated Plots – How to Assess the Contribution of Thalamo-Cortical Networks to Memory). Montaldi et al. (2006) found that activity in the dorsomedian thalamus correlated with familiarity self-reported confidence, although the same region was equally activated during familiarity based and recollection-based judgments. Kafkas and Montaldi (2012) reported greater dorsomedian thalamic activity during high-confidence familiarity trials than during unwanted recollection trials. The same pattern was observed in the orbitofrontal cortex, while the DLPFC and more lateral thalamic clusters were significantly more activated during recollection than familiarity. Intriguingly, the thalamic cluster activated by familiarity was remarkably medial, with the peak located in a position consistent with the putative MDmc or midline territory (coordinates in MNI space: $x = -1$; $y = -15$; $z = 6$). The FMRIB connectivity atlas (Behrens et al., 2003; Johansen-Berg et al., 2005; http://www2.fmrib.ox.ac.uk/connect/) reports the following projection probabilities at these coordinates: sensory cortex 0.02; Occipital cortex 0.10; PFC 0.02; temporal cortex 0.24. This connectivity pattern is compatible with localization of this peak in the MDmc, the midline nuclei, or the AT, because of the relatively high probability of connection with the temporal lobe, but very unlikely in the MDpc. Kafkas and Montaldi (2012) stressed that the dorsomedian thalamic cluster did discriminate hits from misses also in the recollection condition and that, in general, clusters activated during familiarity included subsets of voxels of clusters activated during recollection.

The findings by Kafkas and Montaldi (2012) and Pergola et al. (2013b) agree to some extent. Both studies observed higher thalamic and PFC activation during recall than recognition without recall and an involvement of the MD and the DLPFC in recollection-based recognition, in accord with other fMRI studies (Mottaghy et al., 1999; de Rover et al., 2008; Blumenfeld et al., 2011). On the other hand, the results by Montaldi's group support a role of the MD in familiarity-based recognition, whereas our results suggest that the MDpc is specifically activated by recognition followed by recall. The implications of this discrepancy are discussed in the next section.

Models on the functional architecture of the thalamo-PFC network

Clinical results fail to support the hypothesis of selective familiarity deficits following lesion to the MD. This lack of evidence led Aggleton et al. (2011) to revise their 1999 model. In their multi-effect multi-nuclei (MEMN) model of thalamic contribution to recognition memory, they proposed that the MD, the ILN, and midline nuclei, as well as the pulvinar, may contribute in a graded way to both recollection and familiarity. It was proposed that the MD contributes more to familiarity than to recollection. In light of the data reviewed above, support for the proposal that the MD contributes to familiarity remains shaky, possibly limited to the fMRI results obtained by Montaldi et al. (2006) and Kafkas and Montaldi (2012).

In our opinion there are two possibilities to reconcile the seemingly conflicting neuroimaging findings obtained by Montaldi et al. (2006) and Pergola et al. (2013b). Firstly, the MDpc may support recall, while the MDmc may support familiarity. The distinction between the MDmc and MDpc connectivity patterns has also been advocated by Aggleton (2012) as a discriminant in their functional role; in this perspective, the finding by Kafkas and Montaldi (2012) that a region in the orbitofrontal cortex responded more strongly to familiarity than recollection avails the dissociation between the MDmc and the MDpc, because the MDmc is more strongly connected to the orbitofrontal cortex compared to the MDpc. The dichotomy between the magnocellular and the parvocellular MD may encompass a wider ground than the recollection/familiarity distinction, since the MDmc has also been implicated in reward-based learning. Lesions to the MDmc impair reward-based learning in rodents (Mitchell and Dalrymple-Alford, 2005), and also in monkeys, in particular during acquisition (i.e., initial learning; Mitchell and Gaffan, 2008).

This impairment is also seen after disconnection from the ventromedial PFC (Mitchell et al., 2007), which suggests that it does not depend on the MTL afferents. Removal of cortical neurons produces a greater impairment in memory retrieval than in new learning, whereas subcortical damage produces a greater impairment in new learning than in memory retrieval (Mitchell et al., 2008). Although intriguing, a stark cognitive dissociation between subdivisions of the MD is weakly supported by lesion evidence in animals overall (Mitchell and Chakraborty, 2013). The parcellation of the MD needs further investigation in humans, and should in our opinion be taken into account in future clinical and neuroimaging studies. It is especially important to quantify the extent of the lesions and activations detected to bridge the gap with evidence based on animal studies. Even though the deficits found by Pergola et al. (2012) were relatively mild, quantitative assessments of the lesions revealed that the maximal volume loss in the MDpc was <30% and in most cases unilateral. This percentage is very far from the complete removal of select nuclei that is accomplished with the use of animal models, and it is possible that the role of the MD in memory is underestimated because of the limited extent of the lesions available for study.

A second possibility is that the difference between the studies lies in the tasks used. In particular, the instructions of the task employed by Montaldi et al. (2006) and Kafkas and Montaldi (2012) induced participants to focus their attention on the detection of familiarity during the retrieval phase. This focus on familiarity during retrieval could modulate the cognitive orientation of participants during encoding. The instructions of the task employed by Pergola et al. (2013b), instead, focused attention on associative recall. What kind of memory system is one that changes behavior depending on the conditions set up by the experimenter? The answer is, perhaps, that the MD-PFC network responds to cognitive orientation by setting its function depending on the behavioral goal (Monchi et al., 2001). This hypothesis is consistent with current models of the functional role of the DLPFC (Dobbins and Han, 2006). Accordingly, activation of the thalamo-PFC network is observed not only during retrieval, but also during encoding (Blumenfeld et al., 2011; Pergola et al., 2013b). Following this interpretation, damage to the MD (perhaps the MDpc in particular) would be expected to disrupt goal-directed memory processing more than goal-unrelated memory. This hypothesis remains to be tested.

The functions of the thalamo-PFC network seemingly encompass a wider cognitive domain than episodic memory (see Metzger et al., 2013, for a review). Patients with ischemia in the medial thalamus manifest a spectrum of symptoms including distractibility, aphasia, irritability, disinhibiting, disorganization of perception and thoughts, and executive deficits (Nadeau and Crosson, 1997; Schmahmann, 2003; Van der Werf et al., 2003a; Carrera and Bogousslavsky, 2006; Peterburs et al., 2011; Edelstyn et al., 2012b; Biesbroek et al., 2013). Ischemic lesions in the left medial thalamus, affecting the MD and the ILN, can result in semantic memory deficits in non-aphasic patients (Pergola et al., 2013a). Patients show deficits on a semantic retrieval task requiring activation of a third object from a pair of cues (Kraut et al., 2002b, 2006, 2007; see also Kraut et al., 2002a; Segal et al., 2003; Assaf et al., 2006). As it can be expected, the PFC also plays a role in semantic memory, together with the lateral temporal lobe, the left inferior frontal gyrus, and the occipito-temporo-parietal cortex (Martin and Chao, 2001; Patterson et al., 2007; Hayama and Rugg, 2009; Greenberg and Verfaellie, 2010; Binder and Desai, 2011).

Perhaps even more intriguingly, the thalamo-frontal network has been involved in future thinking. Clinical evidence in this respect is slim, yet Weiler et al. (2010c) documented two cases of patients with mediodorsal ischemic lesions, who showed deficits on a future thinking task. The task required subjects to provide a detailed account of future events in response to a verbal cue. Interestingly, one of the patients appeared free of recognition memory deficits. Weiler et al. (2010a,b) also provided fMRI evidence on the activation of the thalamus, the DLPFC, and the HC during future thinking.

In conclusion, there is strong anatomical evidence supporting a thalamic-PFC network centered in the MD. This network can exert its influence on cognition directly or through the interaction with other brain regions mediated by the PFC and the RTN. Evidence from clinical and neuroimaging studies highlights the importance of this network in episodic memory, particularly with respect to recall. The subunits of the MD show different connectivity patterns and also different activation patterns; however, clinical evidence in this regard is still very limited. Future studies need also to address more systematically whether the deficits are related to the encoding or retrieval phase of memory. It is crucial, in our view, to provide quantitative evidence on the lesions and the activations documented in the MD, and also to consider other components of the thalamo-PFC network (ILN, midline nuclei, RTN) when interpreting the data. Finally, the contribution of the thalamo-PFC system to episodic memory likely depends on task requirements. In light of the seemingly wide function of the thalamo-PFC network in cognition, we suggest that specifically the relevance to the behavioral goal is a variable to take into account in future experimental designs.

THE THALAMO-RETROSPLENIAL NETWORK

In this review we refer by this name to the network that has been introduced by Aggleton and Brown (1999) and extensively characterized from anatomical and functional viewpoints over the last years (for reviews, see: Aggleton et al., 2000; Aggleton and Pearce, 2001; Aggleton, 2008, 2010, 2012; Vann et al., 2009a; Aggleton et al., 2010, 2011). We focused on the thalamus and the RSC for our definition to highlight that in the hypothesized information flow from the HC to the cortex these nodes seem to play a different role, compared to "pre-thalamic" regions. This stance is meant to highlight specializations within the functional unity of the network. In general, however, we use the term "thalamo-RSC" network to indicate the whole connectivity pattern including the HC, the fornix, the mammillary bodies, the MTT, the AT (including the laterodorsal nucleus), the thalamo-RSC connections, and the RSC (including the posterior cingulate cortex).

To briefly summarize the anatomy of the network, also schematized in **Figure 3**, hippocampal efferents run from the subiculum through the fornix to reach the mammillary bodies and the AT (Vann and Aggleton, 2004; Vann, 2010), even though some MTL fibers reach the anterior midline of the thalamus through the inferior thalamic peduncle (Aggleton, 2012). The mammillary

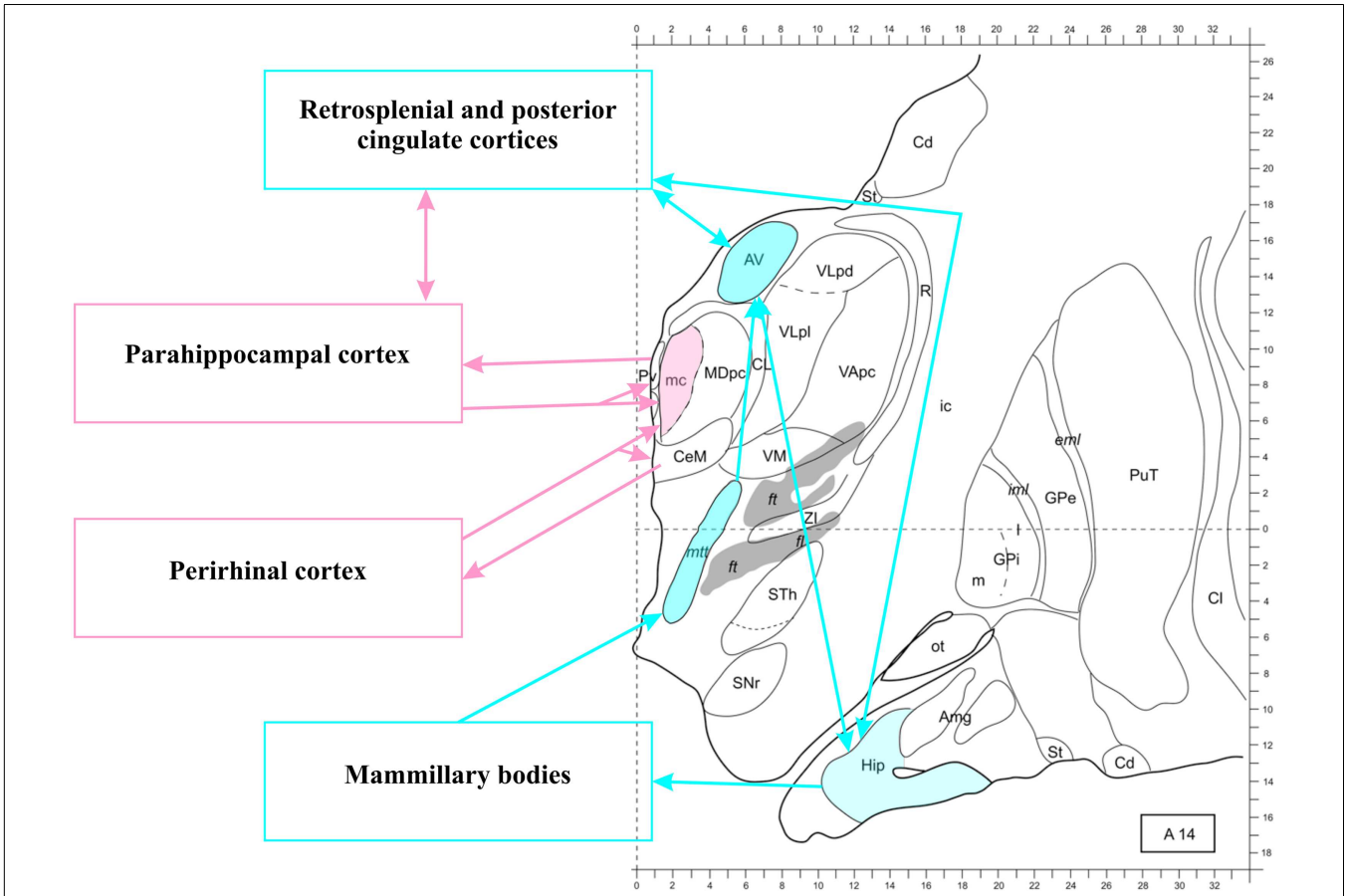


FIGURE 3 | The thalamo-retrosplenial cortical network. Transversal section 14 mm anterior to the posterior commissura. The anterior thalamus, the hippocampus, and the retrosplenial/posterior cingulate cortices form a loop (see Aggleton, 2012, for further details). The magnocellular mediodorsal nucleus (MDmc) does not receive projection from the hippocampus, but from other structures of the medial temporal lobe (including the amygdala, as shown in **Figure 2**). The midline nuclei (not colored) receive and send back projections from all medial temporal lobe structures. Note that connections between medial temporal lobe structures are not shown, see **Figure 1** for an illustration. Modified from Morel (2007). Abbreviations: Amg, amygdala; AV, anteroventral nucleus; Cd, caudate nucleus; CL, centrolateral nucleus; Cl, claustrum; eml, external medullary lamina; ft, fasciculus thalamicus; ic, internal capsula; iml, internal medullary lamina; GPe, globus pallidum, pars externa; GPi, globus pallidum, pars interna; Hip, hippocampus; MD, mediodorsal nucleus; MDpc, parvocellular MD; mtt, mammillothalamic tract; ot, olfactory tubercle; PuT, putamen; Pv, paraventricular nucleus; R, reticular thalamic nucleus; SNr, substantia nigra, pars reticulate; St, striatum; STh, subthalamic nucleus; VApc, ventral anterior nucleus, parvocellular portion; VLpd, ventrolateral nucleus, posterior dorsal subunit; VLpl, posterior lateral subunit; VM, ventromedial nucleus; Zl, zona incerta.

bodies also project to the AT (Vann et al., 2007). The AT, in turn, sends direct projections to the HC through the fornix and also through the cingulum bundle (Aggleton et al., 2010), giving off collaterals in the cingulate cortex. An important intermediate station in the cingulate cortex is the RSC (Morris et al., 1999), which communicates reciprocally with the AT and the HC.

Although the network has been analyzed in greater detail in animal models, results from fMRI studies yielded consistent evidence for RSC activation during recognition memory, together with the lateral parietal cortex (Wagner et al., 2005; Pustina et al., 2012). These regions are thought to belong to the so-called "default mode network" (DMN), which also includes the HC and the ventromedial PFC, and is probably involved in associative processing (Raichle et al., 2001; Vincent et al., 2006; Bar, 2007; Bar et al., 2007; Mason et al., 2007). The existence of a default mode or resting state network was first discussed by Gusnard and Raichle (2001). The specific features of this network have been studied extensively since this time, the most consistent finding being that the DMN is more active during rest than during task performance. Bar et al. (2007) suggested that the DMN is also involved in processing contextual associations, and has thus been named "context network." It has been shown that the DMN is recruited when subjects are using an associative strategy to encode items (Cavanna and Trimble, 2006; Peters et al., 2009). More in general, DMN regions have been reported to support stimulus-independent processing (McGuire et al., 1996; Christoff et al., 2004) and mind-wandering (Mason et al., 2007), although recent results more tightly link its activity to declarative memory (Shapira-Lichter et al., 2013). The thalamo-RSC network discussed in this review appears to be a subcomponent of the DMN network that is most convincingly related to episodic memory processing.

As far as recall is concerned, there is general agreement that integrity of all nodes and tracts of this pathway is critical (Park et al., 2007; Vann et al., 2007, 2009a,b; Vann and Albasser, 2009; Aggleton et al., 2010; Carlesimo et al., 2011). In spite of this consensus, the individual contributions of its components are still under investigation. The AT seem to exert its influence especially over the cingulate cortex and the RSC in particular. Garden et al. (2009) demonstrated decrease of synaptic plasticity in the RSC following AT lesions in rodents. Interestingly, no overt modulation of the electrophysiological response of single receptors occurred, suggesting indirect physiological effects. Evidence from studies targeting genetic expression shows that lesions to the AT result in under regulation of select genes' expression in the RSC (reviewed by Vann and Albasser, 2009; Aggleton, 2010). The tight link between the AT and the RSC is supported by evidence that, across species, the degree of differentiation and the size of the AT correlates with the degree of differentiation in the RSC (reviewed by Jones, 2007). Since Aggleton and Brown (1999) proposal, the AT has been assumed to extend the hippocampal function. This tenet is certainly warranted and well-grounded on solid evidence. However, we will argue that the AT also shows a contribution to memory that is different from that operated by the HC, and perhaps more linked to the modulation they exert on the RSC.

Clinical evidence

The findings mentioned from animal models appear to extend to humans. It has been shown that RSC activity decreases after lesion in the AT (Fazio et al., 1992; Reed et al., 2003; Clarke et al., 1994). Amnesia following damage to the RSC is a well-known phenomenon (reviewed by Vann et al., 2009a; Aggleton, 2010). Damage to the AT also induces amnesia. Harding et al. (2000), in a post-mortem study, found that in alcoholics diagnosed with Wernicke–Korsakoff syndrome cell loss in the AT was the best predictor for amnesia. Disruption of the MTT and the fornix similarly causes recall deficits (Carlesimo et al., 2007; Cipolotti et al., 2008; Tsivilis et al., 2008; Rudebeck et al., 2009). Hence Aggleton and Brown (1999) and Aggleton et al. (2011) proposed that the thalamo-RSC network acts as a unitary recall system, and that damage to any node of the network will cause amnesia.

There is general agreement that lesion to the AT causes recall deficits that resemble the consequences of HC lesion, yet these deficits are surprisingly poorly characterized in neuropsychological literature. We systematically reviewed all stroke reports of memory deficits following *lesions to the AT with spared MD and sufficient neuropsychological assessment of memory*. Results are shown in **Table 2** (see footnote 4, for the criteria used).

We were able to find only six studies that met our criteria, for a total of 16 patients. Data are so scarce because usually AT damage follows an infarct of the tuberothalamic artery; however, the same artery supplies the rostro-lateral part of the MD, especially the MDpc (Schmahmann, 2003). Damage to the MD is assumed to occur in particular following paramedian infarcts, but an analysis including 19 patients with thalamic stroke found no significant difference in the volume lost in the MD following paramedian and tuberothalamic stroke (Pergola et al., 2013c). This may help explain why memory deficits are similar between patients with different etiology (Pergola et al., 2012).

The cases available support the notion that lesion to the AT disproportionately impairs recall over recognition memory (**Table 2**, columns V and VI). Although the MD-PFC connections could have been involved because of damage to the anterior thalamic radiation, there was no evidence of direct damage to the MD in the cases reviewed.

Next, we asked whether these reports supported the assumption that damage to the AT disrupts the function of the HC. Based on the HC-AT connectivity, Van der Werf et al. (2003a) proposed that impairment after AT lesions derives from defective encoding. The RSC, instead, is mostly activated at retrieval (Wiggs et al., 1999; Huijbers et al., 2012, 2013), so we used neuropsychological clues of disrupted encoding or retrieval to inform our analysis.

Although the sample size is very small, 15 out of 16 cases showed evidence of retrieval deficits. Some cases showed encoding deficits only in the acute phase of the disease (i.e., the first week after lesion onset). Hence we found no published evidence of stable memory deficits that could be attributed to defective encoding following selective lesions to the AT. For 13 cases (Hanley et al., 1994; Ghika-Schmid and Bogousslavsky, 2000) the deficits were explicitly interpreted as retrieval-dependent. This conclusion, however, remains a working hypothesis in light of the confounds that also some of these studies present (**Table 2**, gray background) and because of the few cases available. We suggest that future clinical studies should employ tests that allow discrimination of encoding and retrieval deficits and/or use neuroimaging techniques to study the functional consequences of selective lesion to the AT.

Neuroimaging evidence

The phase of activation of the DMN regions, i.e., encoding or retrieval, is a currently debated controversy in the neuroimaging community. There is large consensus on the paramount role of the HC in episodic encoding; evidence on the involvement of the HC in retrieval is more conflicting, since only some of the numerous neuroimaging studies on the role of the HC in episodic memory did find significant activations during retrieval. When activation of the HC during retrieval was observed, an interference of incidental encoding processes during retrieval could not be ultimately ruled out (Stark and Okado, 2003; Huijbers et al., 2009).

Reas and Brewer (2013) performed a parametric analysis of BOLD activation during retrieval, using response times as a proxy for the duration of retrieval search. The authors found that activation of the HC was negatively correlated with response times. The same pattern applied to the medial PFC, posterior cingulate, and inferior parietal cortex. The same regions increased their reciprocal connectivity during successful *incidental* encoding. The authors interpreted this pattern as a deactivation induced by effortful retrieval, in the view of competition for cognitive resources between encoding and retrieval (Huijbers et al., 2009). Interestingly, however, the thalamus (anterior and medial, as can be judged based on Figure 4 by Reas and Brewer, 2013; no coordinates were reported) showed a positive correlation with response times, hence it was involved in effortful retrieval according to authors' interpretation. This evidence suggests that in the thalamo-RSC network there is a parcellation of labor, with the thalamic node performing somewhat different operations compared to the HC and RSC.

Table 2 | Clinical literature on cases with lesion to the anterior thalamic nuclei.

I. Article	II. Laterality	III. Phase of lesion at test	IV. MTT involvement	V. Recall	VI. Recognition	VII. Encoding deficits	VIII. Retrieval deficits	IX. Comments
Hankey and Stewart-Wynne (1988)	L	Acute	YES	Impaired	NA	Immediate recall deficits	–	Post-mortem confirmation of lesion localization
Ott and Saver (1993)[a]	L	Acute and chronic (<1Y)	Perhaps	Impaired	NA	–	Apparent deficit only after delay	Follow-up after 5 months from onset revealed an *additional lesion in the caudate nucleus. MD could have been affected*
Clarke et al. (1994)	L	Acute and chronic (<1Y)	YES	Impaired in the verbal domain	Impaired in the verbal domain	–	Short-term memory was spared	Sensitivity to interference. ILN clearly involved. Posterior cingulate cortex showed hypometabolism
Hanley et al. (1994, 2001)[b]	L	Chronic (>1Y)	YES	Impaired	Spared	–	Deficit interpreted as retrieval-dependent	*Involvement of the fornix and the caudate nucleus*
Ghika-Schmid and Bogousslavsky (2000)	L (eight cases), R (four cases)	Acute, sub-acute, and chronic (<1Y)	YES	Impaired	Mildly impaired	Immediate recall deficits in the acute phase	Deficit more evident after delay. Repeated exposure did not improve performance. Confabulations, intrusions, false memory during the acute and sub-acute phases	Palipsychism in the acute phase, sensitivity to interference, word finding difficulties

Only studies in which no clear evidence of damage to the mediodorsal nucleus was found were included. Shaded rows highlight studies in which confounding factors should be considered when evaluating results. Confounding factors are written in italic font. Acute phase: ≤1 week after lesion onset; sub-acute phase: 1 week < lesion-test interval ≤2 months; chronic phase: >2 months after lesion onset.

ILN, intralaminar thalamic nuclei; L, left-sided lesion; MD, mediodorsal thalamic nucleus; MTT, mammillothalamic tract; NA, not assessed; P, patient; R, right-sided lesion; Y, year.

[a] *One case with anterior thalamic lesion was considered.*

[b] *The lesion was consequent to rupture of an aneurysm.*

Within the thalamus, different regions are activated in different phases of the memory process. The parcellation of the thalamic activation performed by Pergola et al. (2013b) revealed that the AT was selectively active during retrieval. The contrast used compared recognition cues characterized by post-scanning successful recall of the unique associations studied with cues characterized by no subsequent recall. Therefore the findings are in line with the role of the AT in recall. The activation appeared confined to the retrieval phase, and no voxels were activated at group level during encoding. The connectivity pattern of the activated voxels, assessed using established connectivity atlases, appeared consistent with the localization of the clusters in the AT. Finally and most importantly, activation in the putative region of the AT (defined on the basis of an anatomical atlas) correlated with individual recall scores during retrieval, and not during encoding. This evidence does not imply that the AT are inactive during encoding: it is possible that the AT were equally active during successful and unsuccessful encoding, hence preventing detection of significant clusters. However, the finding that inter-individual variability in the activation of the AT during retrieval correlates with recall performance suggests that the AT play an autonomous role during this phase of memory processing.

As we also argued for the thalamo-PFC network in Section "The Thalamo-Prefrontal Network," the thalamo-RSC network has been implicated in wider cognitive functions than recall. It is debated whether the involvement of the DMN is exclusive of memory, or extends to endogenous processing more in general. Tasks without overt demand for memory processing appear to recruit the DMN, including for instance theory of mind (Buckner and Carroll, 2007) and self-referential processing (Johnson et al., 2002). The neural network that supports semantic knowledge related to the self includes the anterior and posterior cingulate cortices as well as the RSC (Gobbini et al., 2004; Donix et al., 2010). However, the same areas are activated even to a greater extent, together with the anteromedial PFC, by episodic autobiographical memory (Levine, 2004; Levine et al., 2004). A recent meta-analysis on neural correlates of autobiographical memory highlighted the common participation of the thalamus, the RSC, the anterior cingulate, and the medial PFC in both episodic and semantic aspects of self-referenced memory (Martinelli et al., 2012). By comparing directly mnemonic and non-mnemonic tasks, Shapira-Lichter et al. (2013) could show that the RSC was more activated during mnemonic processing, both episodic and semantic.

These pieces of evidence suggest that the thalamo-RSC network could constitute a possible *trait d'union* between episodic and semantic memory; on the other hand, they also point to differences in the contribution of the individual nodes of the network to memory. We suggest that the interaction between the AT and the RSC in particular deserves more investigation in humans, and we put forward working hypotheses on the functional specialization of these regions in the next section.

Models on the functional architecture of the thalamo-RSC network

Functional dissociations between the nodes of the thalamo-RSC network have been examined by Huijbers et al. (2012). Authors highlighted that the posterior cingulate and retrosplenial regions include a number of different areas that also show different connectivity patterns, and for this reason several models fail to account exhaustively for RSC activation in fMRI studies. Given that also the AT present heterogeneous connectivity patterns with the hippocampal subfields (reviewed by Aggleton, 2012), it is possible that the thalamo-RSC network consists of multiple pathways partially segregated with respect to their connectivity and function.

In general, the thalamo-RSC network, as part of the DMN, likely subserves associative memory and particularly recall, as documented by a large body of evidence. Work with animal models suggested that the commonalities between impairments observed following HC and AT damage may depend on the particular task used to assess memory (Sziklas and Petrides, 1999, 2004); it is also possible that the RSC constitutes a non-fornical pathway for bilateral communication between the HC and the AT (Henry et al., 2004; Dumont et al., 2010). Evidence from animal studies therefore presents commonalities and differences with respect to the HC, AT, and RSC contribution to memory. Evidence from clinical and neuroimaging studies suggests that the phase of activation – i.e., retrieval – of the AT and RSC is different from what is typically found for the HC, i.e., encoding.

It has thus been suggested that the AT and the RSC are involved in activating and maintaining stored perceptual representations during retrieval (von Zerssen et al., 2001). This proposal would explain why cued recall is required to elicit this activity: recognition by itself does not require activation and maintenance of perceptual representations. This hypothesis assumes a role of the AT during retrieval that is consistent with the evidence reviewed. Vilberg and Rugg (2012) studied the different activation patterns between transient and sustained activation as a function of the duration of maintenance of the representations (analysis focused on the retrieval phase). They did not find activations in the thalamus (although this may partly depend on scanning parameters), but they found that the HC and the RSC were only transiently activated during retrieval. Their findings therefore do not lend direct support to the idea that the HC-RSC network contributes to representation maintenance.

Another intriguing possibility is provided by the Multiple memory Trace Theory (Moscovitch et al., 2005), which predicts that memory retrieval entails the cumulative generation of multiple memory traces that somewhat differ from the original memory trace. In particular, new memory traces are more schematic and more dependent on the RSC (Hirshhorn et al., 2012), while they become progressively independent from the HC. This theoretical framework requires the existence of brain regions intermediate between the HC and the neocortex that transform the memory traces and establish the information originally encoded by the HC into neocortical areas. Also on the basis of neurophysiological findings reviewed below, we propose that the features of the AT (in particular, the regulation of RSC plasticity) match the requirements to subserve this function. In this view, the AT-RSC connections would underlie the generation of multiple memory traces, a role that includes retrieval processes (of the original memory trace) and re-encoding (generation of novel memory traces); on the cognitive side, this information flow could be a relevant path for the conversion of episodic into semantic memory traces. Testing this working hypothesis will require a deeper understanding

of the temporal dynamics of network activations, in line with the approach followed by Vilberg and Rugg (2012). Rather than focusing on the magnitude of activations in the nodes of the network, it is necessary to collect more information on the duration of the activations – an approach that would match the focus on long-term potentiation (LTP) found in neurophysiology.

CONSEQUENCES OF DISRUPTION OF THE THALAMO-PFC AND THALAMO-RSC NETWORKS IN PSYCHIATRIC DISORDERS

Thalamic neuropathology, especially of ischemic and degenerative etiology, has been thoroughly studied in connection with memory deficits (reviewed by Kopelman, 2002; Schmahmann, 2003; Carrera and Bogousslavsky, 2006; Carlesimo et al., 2011). More recently, evidence is accumulating that also psychiatric conditions might include thalamo-cortical dysfunction as a salient feature of their neuropathological picture.

Patients with schizophrenia, in particular, show structural and functional abnormalities in the HC, PFC, and the thalamus. The cognitive profile that accompanies the structural and functional peculiarities of schizophrenia is characterized, among other symptoms, by episodic memory deficits that constitute one of the most impaired aspects of the cognitive profile (Saykin et al., 1991; Mitropoulou et al., 2002; D'Argembeau et al., 2008; Minzenberg et al., 2009). The episodic memory impairment is more evident on recall than on recognition (Pelletier et al., 2005; Thoma et al., 2006; Libby et al., 2013). The weak dependence of the deficits on the duration of the study-test delay led to the hypothesis that the impairments relate to encoding rather than retrieval (Aleman et al., 1999; Gold et al., 2000; Dickinson et al., 2007).

The deficits displayed by patients with schizophrenia are thus suggestive of a dysfunctional thalamo-PFC network (Kuperberg, 2008; Mitchell and Johnson, 2009; Blumenfeld et al., 2011; Libby et al., 2013). Beside the amount of data involving the PFC in the pathology (reviewed by Bertolino and Blasi, 2009), post-mortem studies found specific cell loss in the MD of patients with schizophrenia (Young et al., 2000; Byne et al., 2002), and especially of its parvocellular portion (Popken et al., 2000; reviewed by Byne et al., 2009). Other reports highlighted altered metabolism in the MD and ILN of patients with schizophrenia (Hazlett et al., 2004). Drugs targeting the D2 dopaminergic receptor improve the symptomatology, and the MD presents a high density of D2 receptors (Rieck et al., 2004; Vogt et al., 2008). This feature characterizes primates compared to rodents (Garcia-Cabezas et al., 2009). In healthy subjects, low density of D2 receptors in the thalamus has been related to high creativity in a positron emission tomography study (de Manzano et al., 2010). Dysfunction and decreased connectivity of the MDmc and the orbitofrontal PFC to which it projects have been related to the psychotic symptoms of schizophrenia (Popken et al., 2000; Kubota et al., 2013). The involvement of the MDpc, on the other hand, has been claimed to relate to the cognitive impairments shown by patients with schizophrenia (reviewed by Alelú-Paz and Giménez-Amaya, 2008; Pakkenberg et al., 2009).

Interestingly, the critical alterations in the brain of patients with schizophrenia that affect the networks described in this review, and the thalamo-PFC in particular, are not related to acute damage in a single node of the network. Schizophrenia has been characterized as a neurodevelopmental disorder. In this framework, symptoms of schizophrenia can be thought of as a model of progressive thalamo-cortical dysfunction, with a strong genetic component (Bertolino and Blasi, 2009; Blasi et al., 2013). Accordingly, the neuroimaging literature is rich of evidence on dysfunctional activation and connectivity of the thalamo-PFC network in patients with schizophrenia and also in healthy controls with genetic risk for schizophrenia (Hariri et al., 2003; Bertolino et al., 2008; Di Giorgio et al., 2012; Anticevic et al., 2013). Functional connectivity studies have established altered coupling between the HC and the lateral PFC as a correlate of genetic risk for schizophrenia (Bertolino et al., 2006; Tunbridge et al., 2013).

Altered coupling of the HC and the DLPFC is a notable finding, because the HC is more strongly connected to the ventromedial and orbitofrontal PFC, than to the DLPFC. Based on the thalamo-cortical networks outlined in this review, it is plausible that a transthalamic route involving the MDpc, the RTN, and the MDmc/midline nuclei mediates the interaction between the two brain regions. Cholvin et al. (2013) found evidence of this functional circuitry in rodents; Klingner et al. (2013) obtained results consistent with this suggestion using resting state fMRI. The MDpc-DLPFC connectivity could modulate activity in the RTN, which is able to regulate the midline thalamic nuclei directly projecting to the HC. Matching this hypothesis, Dauvermann et al. (2013) showed decreased MD-PFC connectivity during a verbal fluency task in healthy participants with high genetic risk for schizophrenia, as assessed through non-linear Dynamic Causal Modeling. The effect was greatest for patients also showing symptoms of psychosis.

In summary, the study of the pathophysiology of schizophrenia offers the opportunity of further insight into the physiological and molecular properties of the thalamo-PFC and the thalamo-RSC networks. The next section will go more in detail in the putative mechanisms that might underlie their role in episodic memory.

POSSIBLE MECHANISMS OF THE THALAMO-CORTICAL CONTRIBUTION TO MEMORY AND RELATED PATHOLOGIES

The thalamus is considered to serve as an interface between subcortical structures and the cortex and basal ganglia. It has been described as a "searchlight" (Crick, 1984; Smythies, 1997), an "enhancer" (LaBerge, 1997), and a "focuser" (Van der Werf et al., 2003a). Research has partially discounted the unitary views in recent years, placing emphasis on the diversity of the thalamic nuclei (Sherman and Guillery, 2002).

In this respect it is noteworthy that some thalamic nuclei receive their driving inputs from non-cortical regions (first-order nuclei; e.g., the AT), while other nuclei, such as the MD and the pulvinar, receive their driving input from the cortex, particularly from the V cortical layer. Since these driver inputs do not synapse in the RTN, but they do synapse on subcortical effector nuclei, it has been proposed that these cortico-thalamic connections bear information on planned actions, that is then relayed by the thalamus to other cortical regions (Guillery and Sherman, 2011; Sherman and Guillery, 2011). This information route is called "transthalamic" and is hypothesized to supply upstream cortical regions with information about the signals they are about to receive from

downstream cortical regions, particularly with respect to action execution (Byne et al., 2009). Given the size and conductance of cortico-thalamic and thalamo-cortical fibers it is even possible that the transthalamic route is faster than direct cortico-cortical communication (Salami et al., 2003). The next paragraphs will briefly sketch possible mechanisms of the thalamo-cortical contribution to memory, with mention of the most recent evidence on the topic.

PACEMAKER

The connectivity pattern of the MD enables it to mediate transthalamic communication between temporal and prefrontal regions, as well as between lateral prefrontal subregions. The role of thalamic nuclei in entraining cortical oscillations is well-recognized (Steriade, 2006; Sherman, 2007), and more recent evidence supports the involvement of the MD in particular in regulating PFC oscillations during memory processes. By using a procedure to reversibly disconnect the MD and the PFC in mice, Parnaudeau et al. (2013) demonstrated memory deficits in a delayed non-matching to sample task at long delays (see Aggleton and Brown, 1999, for a discussion about the use of this task to assess recognition memory in rodents). Performance was impaired in trained animals, suggesting that the deficit was not limited to the encoding phase. The critical range of frequencies for the MD-PFC connectivity was the beta and gamma range.

The dynamics of the MD-prefrontal interplay in humans have been recently reported by Staudigl et al. (2012), who studied a patient with epilepsy by means of intracranial recordings. The authors demonstrated a link between thalamic activity in the putative MD territory during retrieval and scalp frontal beta-frequency modulation in the time window 300–500 ms post-stimulus onset. This time window is commonly associated to a frontal old/new effect in the ERP literature (reviewed by Paller et al., 2007; Rugg and Curran, 2007). Strikingly, Staudigl et al. (2012) could show that the direction of the signal was thalamo-cortical. Additionally, the authors reported cross-frequency coupling relating the power in the beta range with power in the gamma frequency-range (Staudigl et al., 2012). Unfortunately, the study did not report activity during encoding and concluded that the MD is more involved in retrieval compared to the AT, a finding to our knowledge not supported by any evidence based on studies with humans (as discussed, see The Thalamo-Retrosplenial Network). Notwithstanding the difficulties of locating electrodes in the thalamus of the epileptic patient, the AT are first-order nuclei projecting to deep brain regions, so several synapses could be needed before the signal reaches the outer cortex, which is the main source of scalp potentials. Fitzgerald et al. (2013) extended these findings by showing a more complex pattern of functional connectivity between the thalamus and the PFC. The interactions included phase-amplitude and amplitude-amplitude coupling and were established based on data from three patients receiving deep brain stimulation.

This evidence suggests that the contribution of the thalamo-PFC network to episodic memory can be mediated by modulation of cortical oscillations induced by thalamic activity. Disruption of thalamo-PFC connectivity also characterizes schizophrenia: in the study by Anticevic et al. (2013), the most prominent locus of thalamic dysconnectivity was centered on the MD.

PLASTICITY DEVICE

Aggleton et al. (2011) proposed that the AT may be part of a triangular circuitry including also the HC and the cingulate and prefrontal cortices. Triangular connections enable the setup of coincidence detection systems (Jones, 2007) based on LTP. In rodents, LTP can be induced in the cingulate and PFC by co-activation of convergent hippocampal and thalamic afferents (Gigg et al., 1992, 1994). Further evidence from animal studies suggests that the AT modulates plasticity in the RSC (Garden et al., 2009). As previously mentioned, it can be hypothesized that the cingulate (especially RSC) and medial prefrontal LTP could foster transfer of memory traces from the HC to the neocortex during retrieval and concurrent re-encoding (Moscovitch et al., 2005; Hirshhorn et al., 2012). A proof of concept for this working hypothesis comes from a study with rats in which modulation of the MD-PFC connectivity was shown to affect prefrontal LTP, resulting in strengthening or decreasing thalamo-cortical connectivity (Bueno-Junior et al., 2012).

Long-term potentiation could therefore be one physiological mechanism underlying the role of thalamo-cortical networks, and especially the thalamo-RSC network, in episodic memory. It is established that LTP is a critical feature of memory formation, and evidence is accumulating in favor of a "plasticity account" for diseases such as schizophrenia (reviewed by Weinberger and Harrison, 2011).

A critical feature of a plasticity regulator is selectivity: enhancing or decreasing signal in general would not be sufficient to afford a selective increase of specific patterns of neural activity. The thalamus, as a complex, is particularly suitable for such a role. The thalamus sends selective as well as widespread projections to the cortex, ending in specific cortical layers (Byne et al., 2009). The convergence of specific (e.g., MD to PFC) and aspecific connections (e.g., ILN to PFC) would provide the basic circuitry necessary for a coincidence detection system (see the core/matrix hypothesis, Jones, 2007) that would be able to modulate plasticity in specific cortical populations. The potential importance of such processes for memory has been shown by Logothetis et al. (2012), who found that increased activation in the HC was accompanied by decreased thalamic activation. The authors proposed that decreased thalamic activity may serve to shield the cortex from interference during memory consolidation. This proposal is particularly intriguing in light of the findings that in the acute phase of ischemia involving the AT patients are especially sensitive to interference (see **Table 2**).

In summary, the effect of the thalamo-cortical interaction could operate at a greater time scale than previously thought, determining long-term changes in connectivity, a suitable mechanism for memory formation and transformation.

SUMMARY

In this article we summarized evidence that beside the medial temporal lobe, two other brain networks are involved in memory processing. These structures are not exclusively bound to memory processes, but also contribute to executive functions and future thinking. The evidence reviewed shows that memory processing at different stages draws on different and also shared resources depending on the required processes.

The thalamo-PFC network has often been mentioned as fundamental for declarative, and especially episodic, memory. Until now, however, it is debated whether it rather plays only an ancillary role with respect to the MTL. We argued that by using tests that specifically tap recall it is possible to reveal the contribution of the thalamo-PFC network to episodic memory. Differently from previous views, we argued that the MD is critical for recall. The field has not sufficiently investigated whether subunits of the MD are functionally segregated, and this remains a task for future experimental scrutiny. Our working hypothesis is that this network is especially involved in goal-directed, as opposed to incidental, memory acquisition. This hypothesis can be tested by comparing incidental against goal-directed encoding, and also by comparing results obtained through tasks that induce different cognitive orientations. Regulating medial temporal and prefrontal oscillations and connectivity are possible mechanisms by which the network could act; these mechanisms have been shown to be dysfunctional in schizophrenia, which in many aspects shows a neuropathophysiology consistent with disruption of the thalamo-PFC network.

The importance of the thalamo-RSC network in recall has met wide consensus. We reviewed evidence that the understanding of the functional unity of this network that dominated the recent literature is changing, following recent discoveries on functional specializations of its nodes. The recruitment of different nodes of the network in different memory stages (encoding and retrieval) is a consistent finding. In particular, clinical and neuroimaging evidence indicates an involvement of the AT and the RSC in the retrieval phase of memory processing. The functional parcellation of the network is particularly interesting in light of models of memory, such as the Multiple Memory Trace theory, that posit the existence of regions governing the information flow from the HC to the neocortex. The thalamo-RSC network appears to be especially fit for this function, possibly mediated by regulation of neocortical plasticity. This hypothesis can be tested by focusing on the duration of activations and on the effects of repeated exposure to stimuli, whose representation passes from episodic- to semantic-like.

We suggest that advancing the field will require a more extensive use of quantitative procedures in the assessment of thalamic lesions and activations, and we share the impression of Metzger et al. (2013) that improving the spatial resolution of imaging methods will greatly enhance our understanding of the function of non-MTL regions in memory. Moreover, we suggest that focusing research on different aspects of recall and their neural determinants rather than on recall/recognition dichotomies will be an effective way to move forward. We are still bound to the statement by James reported at the beginning of this review about empirical design of memory studies: recall seems to be the chief task to study episodic memory.

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REFERENCES

Achim, A. M., and Lepage, M. (2005). Neural correlates of memory for items and for associations: an event-related functional magnetic resonance imaging study. *J. Cogn. Neurosci.* 17, 652–667. doi:10.1162/0898929053467578

Aggleton, J. P. (2008). EPS Mid-Career Award 2006. Understanding anterograde amnesia: disconnections and hidden lesions. *Q. J. Exp. Psychol. (Hove)* 61, 1441–1471. doi:10.1080/17470210802215335

Aggleton, J. P. (2010). Understanding retrosplenial amnesia: insights from animal studies. *Neuropsychologia* 48, 2328–2338. doi:10.1016/j.neuropsychologia.2009.09.030

Aggleton, J. P. (2012). Multiple anatomical systems embedded within the primate medial temporal lobe: implications for hippocampal function. *Neurosci. Biobehav. Rev.* 36, 1579–1596. doi:10.1016/j.neubiorev.2011.09.005

Aggleton, J. P., and Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav. Brain Sci.* 22, 425–444. doi:10.1017/S0140525X99002034

Aggleton, J. P., Dumont, J. R., and Warburton, E. C. (2011). Unraveling the contributions of the diencephalon to recognition memory: a review. *Learn. Mem.* 18, 384–400. doi:10.1101/lm.1884611

Aggleton, J. P., O'Mara, S. M., Vann, S. D., Wright, N. F., Tsanov, M., and Erichsen, J. T. (2010). Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur. J. Neurosci.* 31, 2292–2307. doi:10.1111/j.1460-9568.2010.07251.x

Aggleton, J. P., and Pearce, J. M. (2001). Neural systems underlying episodic memory: insights from animal research. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1467–1482. doi:10.1098/rstb.2001.0946

Aggleton, J. P., Vann, S. D., Denby, C., Dix, S., Mayes, A. R., Roberts, N., et al. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia* 43, 1810–1823. doi:10.1016/j.neuropsychologia.2005.01.019

Aggleton, J. P., Vann, S. D., Oswald, C. J., and Good, M. (2000). Identifying cortical inputs to the rat hippocampus that subserve allocentric spatial processes: a simple problem with a complex answer. *Hippocampus* 10, 466–474. doi:10.1002/1098-1063(2000)10:4<466::AID-HIPO13>3.0.CO;2-Y

Alelú-Paz, R., and Giménez-Amaya, J. M. (2008). The mediodorsal thalamic nucleus and schizophrenia. *J. Psychiatry Neurosci.* 33, 489–498.

Aleman, A., Hijman, R., de Haan, E. H., and Kahn, R. S. (1999). Memory impairment in schizophrenia: a meta-analysis. *Am. J. Psychiatry* 156, 1358–1366.

Allan, K., and Rugg, M. D. (1998). Neural correlates of cued recall with and without retrieval of source memory. *Neuroreport* 9, 3463–3466. doi:10.1097/00001756-199810260-00023

Anticevic, A., Cole, M. W., Repovs, G., Murray, J. D., Brumbaugh, M. S., Winkler, A. M., et al. (2013). Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cereb. Cortex.* doi:10.1093/cercor/bht165

Assaf, M., Calhoun, V. D., Kuzu, C. H., Kraut, M. A., Rivkin, P. R., Hart, J. Jr., et al. (2006). Neural correlates of the object-recall process in semantic memory. *Psychiatry Res.* 147, 115–126. doi:10.1016/j.pscychresns.2006.01.002

Avanzini, G., de Curtis, M., Franceschetti, S., Sancini, G., and Spreafico, R. (1996). Cortical versus thalamic mechanisms underlying spike and wave discharges in GAERS. *Epilepsy Res.* 26, 37–44. doi:10.1016/S0920-1211(96)00037-X

Awipi, T., and Davachi, L. (2008). Content-specific source encoding in the human medial temporal lobe. *J. Exp. Psychol. Learn. Mem. Cogn.* 34, 769–779. doi:10.1037/0278-7393.34.4.769

Badgaiyan, R. D., Schacter, D. L., and Alpert, N. M. (2002). Retrieval of relational information: a role for the left inferior prefrontal cortex. *Neuroimage* 17, 393–400. doi:10.1006/nimg.2002.1219

Bar, M. (2007). The proactive brain: using analogies and associations to generate predictions. *Trends Cogn. Sci.* 11, 280–289. doi:10.1016/j.tics.2007.05.005

Bar, M., Aminoff, E., Mason, M., and Fenske, M. (2007). The units of thought. *Hippocampus* 17, 420–428. doi:10.1002/hipo.20287

Barbas, H., Garcia-Cabezas, M. A., and Zikopoulos, B. (2012). Frontal-thalamic circuits associated with language. *Brain Lang.* 126, 49–61. doi:10.1016/j.bandl.2012.10.001

Barbas, H., Henion, T. H., and Dermon, C. R. (1991). Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. *J. Comp. Neurol.* 313, 65–94. doi:10.1002/cne.903130106

Bastin, C., Linden, M., Charnallet, A., Denby, C., Montaldi, D., Roberts, N., et al. (2004). Dissociation between recall and recognition memory performance in an amnesic patient with hippocampal damage following carbon monoxide poisoning. *Neurocase* 10, 330–344. doi:10.1080/13554790490507650

Baxter, M. G. (2013). Mediodorsal thalamus and cognition in non-human primates. *Front. Syst. Neurosci.* 7:38. doi:10.3389/fnsys.2013.00038

Behrens, T. E., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A., Boulby, P. A., et al. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat. Neurosci.* 6, 750–757. doi:10.1038/nn1075

Bergstrom, Z. M., Henson, R. N., Taylor, J. R., and Simons, J. S. (2013). Multimodal imaging reveals the spatiotemporal dynamics of recollection. *Neuroimage* 68, 141–153. doi:10.1016/j.neuroimage.2012.11.030

Bertolino, A., and Blasi, G. (2009). The genetics of schizophrenia. *Neuroscience* 164, 288–299. doi:10.1016/j.neuroscience.2009.04.038

Bertolino, A., Di Giorgio, A., Blasi, G., Sambataro, F., Caforio, G., Sinibaldi, L., et al. (2008). Epistasis between dopamine regulating genes identifies a nonlinear response of the human hippocampus during memory tasks. *Biol. Psychiatry* 64, 226–234. doi:10.1016/j.biopsych.2008.02.001

Bertolino, A., Rubino, V., Sambataro, F., Blasi, G., Latorre, V., Fazio, L., et al. (2006). Prefrontal-hippocampal coupling during memory processing is modulated by COMT val158met genotype. *Biol. Psychiatry* 60, 1250–1258. doi:10.1016/j.biopsych.2006.03.078

Biesbroek, J. M., Kuijf, H. J., van der Graaf, Y., Vincken, K. L., Postma, A., Mali, W. P., et al. (2013). Association between subcortical vascular lesion location and cognition: a Voxel-Based and Tract-Based Lesion-Symptom Mapping Study. The SMART-MR Study. *PLoS ONE* 8:e60541. doi:10.1371/journal.pone.0060541

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci.* 15, 527–536. doi:10.1016/j.tics.2011.10.001

Bird, C. M., Shallice, T., and Cipolotti, L. (2007). Fractionation of memory in medial temporal lobe amnesia. *Neuropsychologia* 45, 1160–1171. doi:10.1016/j.neuropsychologia.2006.10.011

Blasi, G., Napolitano, F., Ursini, G., Di Giorgio, A., Caforio, G., Taurisano, P., et al. (2013). Association of GSK-3beta genetic variation with GSK-3beta expression, prefrontal cortical thickness, prefrontal physiology, and schizophrenia. *Am. J. Psychiatry* 170, 868–876. doi:10.1176/appi.ajp.2012.12070908

Blumenfeld, R. S., Parks, C. M., Yonelinas, A. P., and Ranganath, C. (2011). Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. *J. Cogn. Neurosci.* 23, 257–265. doi:10.1162/jocn.2010.21459

Blumenfeld, R. S., and Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist.* 13, 280–291. doi:10.1177/1073858407299290

Bogousslavsky, J., Miklossy, J., Deruaz, J. P., Regli, F., and Assal, G. (1986). Unilateral left paramedian infarction of thalamus and midbrain: a clinico-pathological study. *J. Neurol. Neurosurg. Psychiatry* 49, 686–694. doi:10.1136/jnnp.49.6.686

Brown, M. W., Barker, G. R., Aggleton, J. P., and Warburton, E. C. (2012). What pharmacological interventions indicate concerning the role of the perirhinal cortex in recognition memory. *Neuropsychologia* 50, 3122–3140. doi:10.1016/j.neuropsychologia.2012.07.034

Brown, M. W., Warburton, E. C., and Aggleton, J. P. (2010). Recognition memory: material, processes, and substrates. *Hippocampus* 20, 1228–1244. doi:10.1002/hipo.20858

Buckner, R. L., and Carroll, D. C. (2007). Self-projection and the brain. *Trends Cogn. Sci.* 11, 49–57. doi:10.1016/j.tics.2006.11.004

Bueno-Junior, L. S., Lopes-Aguiar, C., Ruggiero, R. N., Romcy-Pereira, R. N., and Leite, J. P. (2012). Muscarinic and nicotinic modulation of thalamo-prefrontal cortex synaptic plasticity [corrected] in vivo. *PLoS ONE* 7:e47484. doi:10.1371/journal.pone.0047484

Burgess, P. W., Gilbert, S. J., and Dumontheil, I. (2007). Function and localization within rostral prefrontal cortex (area 10). *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 887–899. doi:10.1098/rstb.2007.2095

Byne, W., Buchsbaum, M. S., Mattiace, L. A., Hazlett, E. A., Kemether, E., Elhakem, S. L., et al. (2002). Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. *Am. J. Psychiatry* 159, 59–65. doi:10.1176/appi.ajp.159.1.59

Byne, W., Hazlett, E. A., Buchsbaum, M. S., and Kemether, E. (2009). The thalamus and schizophrenia: current status of research. *Acta Neuropathol.* 117, 347–368. doi:10.1007/s00401-008-0404-0

Calabrese, P., Haupts, M., Markowitsch, H. J., and Gehlen, W. (1993). The cognitive-mnestic performance profile of a patient with bilateral asymmetrical thalamic infarction. *Int. J. Neurosci.* 71, 101–106. doi:10.3109/00207459309000597

Cansino, S., Maquet, P., Dolan, R. J., and Rugg, M. D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cereb. Cortex* 12, 1048–1056. doi:10.1093/cercor/12.10.1048

Carlesimo, G. A., Lombardi, M. G., and Caltagirone, C. (2011). Vascular thalamic amnesia: a reappraisal. *Neuropsychologia* 49, 777–789. doi:10.1016/j.neuropsychologia.2011.01.026

Carlesimo, G. A., Serra, L., Fadda, L., Cherubini, A., Bozzali, M., and Caltagirone, C. (2007). Bilateral damage to the mammillo-thalamic tract impairs recollection but not familiarity in the recognition process: a single case investigation. *Neuropsychologia* 45, 2467–2479. doi:10.1016/j.neuropsychologia.2007.03.025

Carrera, E., and Bogousslavsky, J. (2006). The thalamus and behavior: effects of anatomically distinct strokes. *Neurology* 66, 1817–1823. doi:10.1212/01.wnl.0000219679.95223.4c

Cavanna, A. E., and Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583. doi:10.1093/brain/awl004

Cholvin, T., Loureiro, M., Cassel, R., Cosquer, B., Geiger, K., De Sa Nogueira, D., et al. (2013). The ventral midline thalamus contributes to strategy shifting in a memory task requiring both prefrontal cortical and hippocampal functions. *J. Neurosci.* 33, 8772–8783. doi:10.1523/JNEUROSCI.0771-13.2013

Christoff, K., Ream, J. M., and Gabrieli, J. D. (2004). Neural basis of spontaneous thought processes. *Cortex* 40, 623–630. doi:10.1016/S0010-9452(08)70158-8

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., and Sperling, R. A. (2007). Evidence for a specific role of the anterior hippocampal region in successful associative encoding. *Hippocampus* 17, 1071–1080. doi:10.1002/hipo.20340

Cipolotti, L., Bird, C., Good, T., Macmanus, D., Rudge, P., and Shallice, T. (2006). Recollection and familiarity in dense hippocampal amnesia: a case study. *Neuropsychologia* 44, 489–506. doi:10.1016/j.neuropsychologia.2005.05.014

Cipolotti, L., Husain, M., Crinion, J., Bird, C. M., Khan, S. S., Losseff, N., et al. (2008). The role of the thalamus in amnesia: a tractography, high-resolution MRI and neuropsychological study. *Neuropsychologia* 46, 2745–2758. doi:10.1016/j.neuropsychologia.2008.05.009

Clarke, S., Assal, G., Bogousslavsky, J., Regli, F., Townsend, D. W., Leenders, K. L., et al. (1994). Pure amnesia after unilateral left polar thalamic infarct: topographic and sequential neuropsychological and metabolic (PET) correlations. *J. Neurol. Neurosurg. Psychiatry* 57, 27–34. doi:10.1136/jnnp.57.1.27

Corbit, L. H., Muir, J. L., and Balleine, B. W. (2003). Lesions of mediodorsal thalamus and anterior thalamic nuclei produce dissociable effects on instrumental conditioning in rats. *Eur. J. Neurosci.* 18, 1286–1294. doi:10.1046/j.1460-9568.2003.02833.x

Crick, F. (1984). Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl. Acad. Sci. U.S.A.* 81, 4586–4590. doi:10.1073/pnas.81.14.4586

Cross, L., Brown, M. W., Aggleton, J. P., and Warburton, E. C. (2012). The medial dorsal thalamic nucleus and the medial prefrontal cortex of the rat function together to support associative recognition and recency but not item recognition. *Learn. Mem.* 20, 41–50. doi:10.1101/lm.028266.112

Cycowicz, Y. M., Friedman, D., and Snodgrass, J. G. (2001). Remembering the color of objects: an ERP investigation of source memory. *Cereb. Cortex* 11, 322–334. doi:10.1093/cercor/11.4.322

D'Argembeau, A., Raffard, S., and Van der Linden, M. (2008). Remembering the past and imagining the future in schizophrenia. *J. Abnorm. Psychol.* 117, 247–251. doi:10.1037/0021-843X.117.1.247

Daum, I., and Ackermann, H. (1994). Dissociation of declarative and nondeclarative memory after bilateral thalamic lesions: a case report. *Int. J. Neurosci.* 75, 153–165. doi:10.3109/00207459408986299

Dauvermann, M. R., Whalley, H. C., Romaniuk, L., Valton, V., Owens, D. G., Johnstone, E. C., et al. (2013). The application of nonlinear dynamic causal modelling for fMRI in subjects at high genetic risk of schizophrenia. *Neuroimage* 73, 16–29. doi:10.1016/j.neuroimage.2013.01.063

Davachi, L., Mitchell, J. P., and Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2157–2162. doi:10.1073/pnas.0337195100

de Manzano, O., Cervenka, S., Karabanov, A., Farde, L., and Ullen, F. (2010). Thinking outside a less intact box: thalamic dopamine D2 receptor densities are negatively related to psychometric creativity in healthy individuals. *PLoS ONE* 5:e10670. doi:10.1371/journal.pone.0010670

de Rover, M., Petersson, K. M., van der Werf, S. P., Cools, A. R., Berger, H. J., and Fernandez, G. (2008). Neural correlates of strategic memory retrieval: differentiating between spatial-associative and temporal-associative strategies. *Hum. Brain Mapp.* 29, 1068–1079. doi:10.1002/hbm.20445

Di Giorgio, A., Gelao, B., Caforio, G., Romano, R., Andriola, I., D'Ambrosio, E., et al. (2012). Evidence that hippocampal-parahippocampal dysfunction is related to genetic risk for schizophrenia. *Psychol. Med.* 43, 1661–1671. doi:10.1017/S0033291712002413

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2008). The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. *J. Exp. Psychol. Learn. Mem. Cogn.* 34, 730–740. doi:10.1037/0278-7393.34.4.730

Dickinson, D., Ramsey, M. E., and Gold, J. M. (2007). Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch. Gen. Psychiatry* 64, 532–542. doi:10.1001/archpsyc.64.5.532

Dobbins, I. G., Foley, H., Schacter, D. L., and Wagner, A. D. (2002). Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron* 35, 989–996. doi:10.1016/S0896-6273(02)00858-9

Dobbins, I. G., and Han, S. (2006). Isolating rule- versus evidence-based prefrontal activity during episodic and lexical discrimination: a functional magnetic resonance imaging investigation of detection theory distinctions. *Cereb. Cortex* 16, 1614–1622. doi:10.1093/cercor/bhj098

Dobbins, I. G., and Wagner, A. D. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cereb. Cortex* 15, 1768–1778. doi:10.1093/cercor/bhi054

Dolan, R. J., and Fletcher, P. C. (1997). Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388, 582–585. doi:10.1038/41561

Donix, M., Petrowski, K., Jurjanz, L., Huebner, T., Herold, U., Baeumler, D., et al. (2010). Age and the neural network of personal familiarity. *PLoS ONE* 5:e15790. doi:10.1371/journal.pone.0015790

Dumont, J. R., Petrides, M., and Sziklas, V. (2010). Fornix and retrosplenial contribution to a hippocampo-thalamic circuit underlying conditional learning. *Behav. Brain Res.* 209, 13–20. doi:10.1016/j.bbr.2009.12.040

Duzel, E., Cabeza, R., Picton, T. W., Yonelinas, A. P., Scheich, H., Heinze, H. J., et al. (1999). Task-related and item-related brain processes of memory retrieval. *Proc. Natl. Acad. Sci. U.S.A.* 96, 1794–1799. doi:10.1073/pnas.96.4.1794

Edelstyn, N. M., Hunter, B., and Ellis, S. J. (2006). Bilateral dorsolateral thalamic lesions disrupts conscious recollection. *Neuropsychologia* 44, 931–938. doi:10.1016/j.neuropsychologia.2005.08.012

Edelstyn, N. M., Mayes, A. R., Denby, C., and Ellis, S. J. (2012a). Impairment in material-specific long-term memory following unilateral mediodorsal thalamic damage and presumed partial disconnection of the mammillo-thalamic tract. *J. Neuropsychol.* 6, 119–140. doi:10.1111/j.1748-6653.2011.02019.x

Edelstyn, N. M., Mayes, A. R., and Ellis, S. J. (2012b). Damage to the dorsomedial thalamic nucleus, central lateral intralaminar thalamic nucleus, and midline thalamic nuclei on the right-side impair executive function and attention under conditions of high demand but not low demand. *Neurocase.* doi:10.1080/13554794.2012.713497

Eichenbaum, H., and Lipton, P. A. (2008). Towards a functional organization of the medial temporal lobe memory system: role of the parahippocampal and medial entorhinal cortical areas. *Hippocampus* 18, 1314–1324. doi:10.1002/hipo.20500

Eichenbaum, H., Yonelinas, A. P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152. doi:10.1146/annurev.neuro.30.051606.094328

Exner, C., Weniger, G., and Irle, E. (2001). Implicit and explicit memory after focal thalamic lesions. *Neurology* 57, 2054–2063. doi:10.1212/WNL.57.11.2054

Fazio, F., Perani, D., Gilardi, M. C., Colombo, F., Cappa, S. F., Vallar, G., et al. (1992). Metabolic impairment in human amnesia: a PET study of memory networks. *J. Cereb. Blood Flow Metab.* 12, 353–358. doi:10.1038/jcbfm.1992.52

Fitzgerald, T. H., Valentin, A., Selway, R., and Richardson, M. P. (2013). Cross-frequency coupling within and between the human thalamus and neocortex. *Front. Hum. Neurosci.* 7:84. doi:10.3389/fnhum.2013.00084

Fukutake, T., Akada, K., Ito, S., Okuda, T., and Ueki, Y. (2002). Severe personality changes after unilateral left paramedian thalamic infarct. *Eur. Neurol.* 47, 156–160. doi:10.1159/000047974

Garcia-Cabezas, M. A., Martinez-Sanchez, P., Sanchez-Gonzalez, M. A., Garzon, M., and Cavada, C. (2009). Dopamine innervation in the thalamus: monkey versus rat. *Cereb. Cortex* 19, 424–434. doi:10.1093/cercor/bhn093

Garcia-Cabezas, M. A., Rico, B., Sanchez-Gonzalez, M. A., and Cavada, C. (2007). Distribution of the dopamine innervation in the macaque and human thalamus. *Neuroimage* 34, 965–984. doi:10.1016/j.neuroimage.2006.07.032

Garden, D. L., Massey, P. V., Caruana, D. A., Johnson, B., Warburton, E. C., Aggleton, J. P., et al. (2009). Anterior thalamic lesions stop synaptic plasticity in retrosplenial cortex slices: expanding the pathology of diencephalic amnesia. *Brain* 132, 1847–1857. doi:10.1093/brain/awp090

Gardiner, J. M. (1988). Functional aspects of recollective experience. *Mem. Cognit.* 16, 309–313. doi:10.3758/BF03197041

Geraci, L., McCabe, D. P., and Guillory, J. J. (2009). On interpreting the relationship between remember-know judgments and confidence: the role of instructions. *Conscious. Cogn.* 18, 701–709. doi:10.1016/j.concog.2009.04.010

Ghika-Schmid, F., and Bogousslavsky, J. (2000). The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. *Ann. Neurol.* 48, 220–227. doi:10.1002/1531-8249(200008)48:2<220::AID-ANA12>3.3.CO;2-D

Gigg, J., Tan, A. M., and Finch, D. M. (1992). Glutamatergic excitatory responses of anterior cingulate neurons to stimulation of the mediodorsal thalamus and their regulation by GABA: an in vivo iontophoretic study. *Cereb. Cortex* 2, 477–484. doi:10.1093/cercor/2.6.477

Gigg, J., Tan, A. M., and Finch, D. M. (1994). Glutamatergic hippocampal formation projections to prefrontal cortex in the rat are regulated by GABAergic inhibition and show convergence with glutamatergic projections from the limbic thalamus. *Hippocampus* 4, 189–198. doi:10.1002/hipo.450040209

Gobbini, M. I., Leibenluft, E., Santiago, N., and Haxby, J. V. (2004). Social and emotional attachment in the neural representation of faces. *Neuroimage* 22, 1628–1635. doi:10.1016/j.neuroimage.2004.03.049

Gold, J. M., Rehkemper, G., Binks, S. W. III, Carpenter, C. J., Fleming, K., Goldberg, T. E., et al. (2000). Learning and forgetting in schizophrenia. *J. Abnorm. Psychol.* 109, 534–538. doi:10.1037/0021-843X.109.3.534

Greenberg, D. L., and Verfaellie, M. (2010). Interdependence of episodic and semantic memory: evidence from neuropsychology. *J. Int. Neuropsychol. Soc.* 16, 748–753. doi:10.1017/S1355617710000676

Guillery, R. W., and Sherman, S. M. (2011). Branched thalamic afferents: what are the messages that they relay to the cortex? *Brain Res. Rev.* 66, 205–219. doi:10.1016/j.brainresrev.2010.08.001

Gusnard, D. A., and Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2, 685–694. doi:10.1038/35094500

Hampstead, B. M., and Koffler, S. P. (2009). Thalamic contributions to anterograde, retrograde, and implicit memory: a case study. *Clin. Neuropsychol.* 23, 1232–1249. doi:10.1080/13854040902936679

Hankey, G. J., and Stewart-Wynne, E. G. (1988). Amnesia following thalamic hemorrhage. Another stroke syndrome. *Stroke* 19, 776–778.

Hanley, J. R., Davies, A. D. M., Downes, J. J., and Mayes, A. R. (1994). Impaired recall of verbal material following rupture and repair of anterior communicating artery aneurysm. *Cogn. Neuropsychol.* 11, 543–578. doi:10.1080/02643299408251985

Hanley, J. R., Davies, A. D. M., Downes, J. J., Roberts, J. N., Gong, Q. Y., and Mayes, A. R. (2001). Impaired recall of verbal material following rupture and repair of anterior communicating artery aneurysm. *Neuropsychologia* 39, 1003–1010. doi:10.1016/S0028-3932(01)00020-3

Harding, A., Halliday, G., Caine, D., and Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain* 123, 141–154. doi:10.1093/brain/123.1.141

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., et al. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J. Neurosci.* 23, 6690–6694.

Hayama, H. R., and Rugg, M. D. (2009). Right dorsolateral prefrontal cortex is engaged during post-retrieval processing of both episodic and semantic information. *Neuropsychologia* 47, 2409–2416. doi:10.1016/j.neuropsychologia.2009.04.010

Hazlett, E. A., Buchsbaum, M. S., Kemether, E., Bloom, R., Platholi, J., Brickman, A. M., et al. (2004). Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. *Am. J. Psychiatry* 161, 305–314. doi:10.1176/appi.ajp.161.2.305

Henderson, J. M., Williams, C. C., Castelhano, M. S., and Falk, R. J. (2003). Eye movements and picture processing during recognition. *Percept. Psychophys.* 65, 725–734. doi:10.3758/BF03194809

Henke, K., Buck, A., Weber, B., and Wieser, H. G. (1997). Human hippocampus establishes associations in memory. *Hippocampus* 7, 249–256. doi:10.1002/(SICI)1098-1063(1997)7:3<249::AID-HIPO1>3.0.CO;2-G

Henke, K., Weber, B., Kneifel, S., Wieser, H. G., and Buck, A. (1999). Human hippocampus associates information in memory. *Proc. Natl. Acad. Sci. U.S.A.* 96, 5884–5889. doi:10.1073/pnas.96.10.5884

Henry, J., Petrides, M., St-Laurent, M., and Sziklas, V. (2004). Spatial conditional associative learning: effects of thalamo-hippocampal disconnection in rats. *Neuroreport* 15, 2427–2431. doi:10.1097/00001756-200410250-00025

Hirshhorn, M., Grady, C., Rosenbaum, R. S., Winocur, G., and Moscovitch, M. (2012). The hippocampus is involved in mental navigation for a recently learned, but not a highly familiar environment: a longitudinal fMRI study. *Hippocampus* 22, 842–852. doi:10.1002/hipo.20944

Holdstock, J. S., Mayes, A. R., Gong, Q. Y., Roberts, N., and Kapur, N. (2005). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus* 15, 203–215. doi:10.1002/hipo.20046

Holdstock, J. S., Mayes, A. R., Roberts, N., Cezayirli, E., Isaac, C. L., O'Reilly, R. C., et al. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus* 12, 341–351. doi:10.1002/hipo.10011

Huijbers, W., Pennartz, C. M., Cabeza, R., and Daselaar, S. M. (2009). When learning and remembering compete: a functional MRI study. *PLoS Biol.* 7:e11. doi:10.1371/journal.pbio.1000011

Huijbers, W., Schultz, A. P., Vannini, P., McLaren, D. G., Wigman, S. E., Ward, A. M., et al. (2013). The encoding/retrieval flip: interactions between memory performance and memory stage and relationship to intrinsic cortical networks. *J. Cogn. Neurosci.* 25, 1163–1179. doi:10.1162/jocn_a_00366

Huijbers, W., Vannini, P., Sperling, R. A., Pennartz, C. M., Cabeza, R., and Daselaar, S. M. (2012). Explaining the encoding/retrieval flip: memory-related deactivations and activations in the posteromedial cortex. *Neuropsychologia* 50, 3764–3774. doi:10.1016/j.neuropsychologia.2012.08.021

Hurd, Y. L., and Fagergren, P. (2000). Human cocaine- and amphetamine-regulated transcript (CART) mRNA is highly expressed in limbic- and sensory-related brain regions. *J. Comp. Neurol.* 425, 583–598. doi:10.1002/1096-9861(20001002)425:43.0.CO;2-#

Ioannidis, A. E., Kimiskidis, V. K., Loukopoulou, E., Geroukis, T., Vlaikidis, N., and Kosmidis, M. H. (2012). Apathy, cognitive dysfunction and impaired social cognition in a patient with bilateral thalamic infarction. *Neurocase* 19, 513–520. doi:10.1080/13554794.2012.701645

Isaac, C. L., Holdstock, J. S., Cezayirli, E., Roberts, J. N., Holmes, C. J., and Mayes, A. R. (1998). Amnesia in a patient with lesions limited to the dorsomedial thalamic nucleus. *Neurocase* 4, 497–508. doi:10.1093/neucas/4.6.497-a

James, W. (1890). *The Principles of Psychology,* with Introduction by George A. Miller. Cambridge, MA: Harvard University Press, 654 p.

Johansen-Berg, H., Behrens, T. E., Sillery, E., Ciccarelli, O., Thompson, A. J., Smith, S. M., et al. (2005). Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. *Cereb. Cortex* 15, 31–39. doi:10.1093/cercor/bhh105

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., and Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain* 125, 1808–1814. doi:10.1093/brain/awf181

Jones, E. G. (2007). *The Thalamus.* Cambridge: Cambridge University Press.

Kafkas, A., and Montaldi, D. (2012). Familiarity and recollection produce distinct eye movement, pupil and medial temporal lobe responses when memory strength is matched. *Neuropsychologia* 50, 3080–3093. doi:10.1016/j.neuropsychologia.2012.08.001

Kim, A. S., Vallesi, A., Picton, T. W., and Tulving, E. (2009). Cognitive association formation in episodic memory: evidence from event-related potentials. *Neuropsychologia* 47, 3162–3173. doi:10.1016/j.neuropsychologia.2009.07.015

Klein, J. C., Rushworth, M. F., Behrens, T. E., Mackay, C. E., de Crespigny, A. J., D'Arceuil, H., et al. (2010). Topography of connections between human prefrontal cortex and mediodorsal thalamus studied with diffusion tractography. *Neuroimage* 51, 555–564. doi:10.1016/j.neuroimage.2010.02.062

Klingner, C. M., Langbein, K., Dietzek, M., Smesny, S., Witte, O. W., Sauer, H., et al. (2013). Thalamocortical connectivity during resting state in schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* doi:10.1007/s00406-013-0417-0

Kopelman, M. D. (2002). Disorders of memory. *Brain* 125, 2152–2190. doi:10.1093/brain/awf229

Kopelman, M. D., Thomson, A. D., Guerrini, I., and Marshall, E. J. (2009). The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol Alcohol.* 44, 148–154. doi:10.1093/alcalc/agn118

Kraut, M. A., Cherry, B., Pitcock, J. A., Anand, R., Li, J., Vestal, L., et al. (2007). The Semantic Object Retrieval Test (SORT) in amnestic mild cognitive impairment. *Cogn. Behav. Neurol.* 20, 62–67. doi:10.1097/WNN.0b013e3180335f7d

Kraut, M. A., Cherry, B., Pitcock, J. A., Vestal, L., Henderson, V. W., and Hart, J. Jr. (2006). The Semantic Object Retrieval Test (SORT) in normal aging and Alzheimer disease. *Cogn. Behav. Neurol.* 19, 177–184. doi:10.1097/01.wnn.0000213922.41008.22

Kraut, M. A., Kremen, S., Moo, L. R., Segal, J. B., Calhoun, V., and Hart, J. Jr. (2002a). Object activation in semantic memory from visual multimodal feature input. *J. Cogn. Neurosci.* 14, 37–47. doi:10.1162/089892902317205302

Kraut, M. A., Kremen, S., Segal, J. B., Calhoun, V., Moo, L. R., and Hart, J. Jr. (2002b). Object activation from features in the semantic system. *J. Cogn. Neurosci.* 14, 24–36. doi:10.1162/089892902317205302

Kritchevsky, M., Graff-Radford, N. R., and Damasio, A. R. (1987). Normal memory after damage to medial thalamus. *Arch. Neurol.* 44, 959–962. doi:10.1001/archneur.1987.00520210055019

Kubota, M., Miyata, J., Sasamoto, A., Sugihara, G., Yoshida, H., Kawada, R., et al. (2013). Thalamocortical disconnection in the orbitofrontal region associated with cortical thinning in schizophrenia. *JAMA Psychiatry* 70, 12–21. doi:10.1001/archgenpsychiatry.2012.1023

Kuperberg, G. R. (2008). Building meaning in schizophrenia. *Clin. EEG Neurosci.* 39, 99–102. doi:10.1177/155005940803900216

LaBerge, D. (1997). Attention, awareness, and the triangular circuit. *Conscious. Cogn.* 6, 149–181. doi:10.1006/ccog.1997.0305

Lavenex, P., and Amaral, D. G. (2000). Hippocampal-neocortical interaction: a hierarchy of associativity. *Hippocampus* 10, 420–430. doi:10.1002/1098-1063(2000)10:4<420::AID-HIPO8>3.0.CO;2-5

Levine, B. (2004). Autobiographical memory and the self in time: brain lesion effects, functional neuroanatomy, and lifespan development. *Brain Cogn.* 55, 54–68. doi:10.1016/S0278-2626(03)00280-X

Levine, B., Turner, G. R., Tisserand, D., Hevenor, S. J., Graham, S. J., and McIntosh, A. R. (2004). The functional neuroanatomy of episodic and semantic autobiographical remembering: a prospective functional MRI study. *J. Cogn. Neurosci.* 16, 1633–1646. doi:10.1162/0898929042568587

Libby, L. A., Yonelinas, A. P., Ranganath, C., and Ragland, J. D. (2013). Recollection and familiarity in schizophrenia: a quantitative review. *Biol. Psychiatry* 73, 944–950. doi:10.1016/j.biopsych.2012.10.027

Logothetis, N. K., Eschenko, O., Murayama, Y., Augath, M., Steudel, T., Evrard, H. C., et al. (2012). Hippocampal-cortical interaction during periods of subcortical silence. *Nature* 491, 547–553. doi:10.1038/nature11618

Mandler, G. (1980). Recognizing: the judgment of previous occurence. *Psych. Rev.* 87, 252–271. doi:10.1037/0033-295X.87.3.252

Martin, A., and Chao, L. L. (2001). Semantic memory and the brain: structure and processes. *Curr. Opin. Neurobiol.* 11, 194–201. doi:10.1016/S0959-4388(00)00196-3

Martinelli, P., Sperduti, M., and Piolino, P. (2012). Neural substrates of the self-memory system: new insights from a meta-analysis. *Hum. Brain Mapp.* 34, 1515–1529. doi:10.1002/hbm.22008

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., and Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science* 315, 393–395. doi:10.1126/science.1131295

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn. Sci.* 11, 126–135. doi:10.1016/j.tics.2006.12.003

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Hunkin, N. M., and Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus* 12, 325–340. doi:10.1002/hipo.1111

McCabe, D. P., and Geraci, L. D. (2009). The influence of instructions and terminology on the accuracy of remember-know judgments. *Conscious. Cogn.* 18, 401–413. doi:10.1016/j.concog.2009.02.010

McGuire, P. K., Paulesu, E., Frackowiak, R. S., and Frith, C. D. (1996). Brain activity during stimulus independent thought. *Neuroreport* 7, 2095–2099.

Metzger, C. D., Van der Werf, Y. D., and Walter, M. (2013). Functional mapping of thalamic nuclei and their integration into cortico-striatal-thalamo-cortical loops via ultra-high resolution imaging-from animal anatomy to in vivo imaging in humans. *Front. Neurosci.* 7:24. doi:10.3389/fnins.2013.00024

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., and Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch. Gen. Psychiatry* 66, 811–822. doi:10.1001/archgenpsychiatry.2009.91

Mishkin, M. (1982). A memory system in the monkey. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 298, 83–95. doi:10.1098/rstb.1982.0074

Mitchell, A. S., Baxter, M. G., and Gaffan, D. (2007). Dissociable performance on scene learning and strategy implementation after lesions to magnocellular mediodorsal thalamic nucleus. *J. Neurosci.* 27, 11888–11895. doi:10.1523/JNEUROSCI.1835-07.2007

Mitchell, A. S., Browning, P. G., Wilson, C. R., Baxter, M. G., and Gaffan, D. (2008). Dissociable roles for cortical and subcortical structures in memory retrieval and acquisition. *J. Neurosci.* 28, 8387–8396. doi:10.1523/JNEUROSCI.1924-08.2008

Mitchell, A. S., and Chakraborty, S. (2013). What does the mediodorsal thalamus do? *Front. Syst. Neurosci.* 7:37. doi:10.3389/fnsys.2013.00037

Mitchell, A. S., and Dalrymple-Alford, J. C. (2005). Dissociable memory effects after medial thalamus lesions in the rat. *Eur. J. Neurosci.* 22, 973–985. doi:10.1111/j.1460-9568.2005.04421.x

Mitchell, A. S., and Gaffan, D. (2008). The magnocellular mediodorsal thalamus is necessary for memory acquisition, but not retrieval. *J. Neurosci.* 28, 258–263. doi:10.1523/JNEUROSCI.4922-07.2008

Mitchell, K. J., and Johnson, M. K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory? *Psychol. Bull.* 135, 638–677. doi:10.1037/a0015849

Mitropoulou, V., Harvey, P. D., Maldari, L. A., Moriarty, P. J., New, A. S., Silverman, J. M., et al. (2002). Neuropsychological performance in schizotypal personality disorder: evidence regarding diagnostic specificity. *Biol. Psychiatry* 52, 1175–1182. doi:10.1016/S0006-3223(02)01426-9

Monchi, O., Petrides, M., Petre, V., Worsley, K., and Dagher, A. (2001). Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J. Neurosci.* 21, 7733–7741.

Montaldi, D., and Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus* 20, 1291–1314. doi:10.1002/hipo.20853

Montaldi, D., Spencer, T. J., Roberts, N., and Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus* 16, 504–520. doi:10.1002/hipo.20178

Morel, A. (2007). *Stereotactic Atlas of the Human Thalamus and Basal Ganglia*. New York: Informa Healthcare USA, Inc.

Morris, R., Petrides, M., and Pandya, D. N. (1999). Architecture and connections of retrosplenial area 30 in the rhesus monkey (*Macaca mulatta*). *Eur. J. Neurosci.* 11, 2506–2518. doi:10.1046/j.1460-9568.1999.00672.x

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., et al. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J. Anat.* 207, 35–66. doi:10.1111/j.1469-7580.2005.00421.x

Mottaghy, F. M., Shah, N. J., Krause, B. J., Schmidt, D., Halsband, U., Jancke, L., et al. (1999). Neuronal correlates of encoding and retrieval in episodic memory during a paired-word association learning task: a functional magnetic resonance imaging study. *Exp. Brain Res.* 128, 332–342. doi:10.1007/s002210050853

Murray, L. J., and Ranganath, C. (2007). The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *J. Neurosci.* 27, 5515–5522. doi:10.1523/JNEUROSCI.0406-07.2007

Nadeau, S. E., and Crosson, B. (1997). Subcortical aphasia. *Brain Lang.* 58, 355–402. doi:10.1006/brln.1997.1810

Neufang, M., Heinze, H. J., and Duzel, E. (2006). Electromagnetic correlates of recognition memory processes. *Clin. EEG Neurosci.* 37, 300–308. doi:10.1177/155005940603700407

Newell, B. R., and Dunn, J. C. (2008). Dimensions in data: testing psychological models using state-trace analysis. *Trends Cogn. Sci.* 12, 285–290. doi:10.1016/j.tics.2008.04.009

Ott, B. R., and Saver, J. L. (1993). Unilateral amnesic stroke. Six new cases and a review of the literature. *Stroke* 24, 1033–1042. doi:10.1161/01.STR.24.7.1033

Pakkenberg, B., Scheel-Kruger, J., and Kristiansen, L. V. (2009). Schizophrenia; from structure to function with special focus on the mediodorsal thalamic prefrontal loop. *Acta Psychiatr. Scand.* 120, 345–354. doi:10.1111/j.1600-0447.2009.01447.x

Paller, K. A., Lucas, H. D., and Voss, J. L. (2012). Assuming too much from 'familiar' brain potentials. *Trends Cogn. Sci.* 16, 313–315. doi:10.1016/j.tics.2012.04.010

Paller, K. A., Voss, J. L., and Boehm, S. G. (2007). Validating neural correlates of familiarity. *Trends Cogn. Sci.* 11, 243–250. doi:10.1016/j.tics.2007.04.002

Park, K.-C., Yoon, S.-S., Chang, D. I., Chung, K.-C., Ahn, T.-B., Ku, B. D., et al. (2007). Amnesic syndrome in a mammillothalmic tract infarction. *J. Korean Med. Sci.* 22, 1094–1097. doi:10.3346/jkms.2007.22.6.1094

Parnaudeau, S., O'Neill, P. K., Bolkan, S. S., Ward, R. D., Abbas, A. I., Roth, B. L., et al. (2013). Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. *Neuron* 77, 1151–1162. doi:10.1016/j.neuron.2013.01.038

Patterson, K., Nestor, P. J., and Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat. Rev. Neurosci.* 8, 976–987. doi:10.1038/nrn2277

Pelletier, M., Achim, A. M., Montoya, A., Lal, S., and Lepage, M. (2005). Cognitive and clinical moderators of recognition memory in schizophrenia: a meta-analysis. *Schizophr. Res.* 74, 233–252. doi:10.1016/j.schres.2004.08.017

Pergola, G., Bellebaum, C., Gehlhaar, B., Koch, B., Schwarz, M., Daum, I., et al. (2013a). The involvement of the thalamus in semantic retrieval: a clinical group study. *J. Cogn. Neurosci.* 25, 872–886. doi:10.1162/jocn_a_00364

Pergola, G., Ranft, A., Mathias, K., and Suchan, B. (2013b). The role of the thalamic nuclei in recognition memory accompanied by recall during encoding and retrieval: an fMRI study. *Neuroimage* 74, 195–208. doi:10.1016/j.neuroimage.2013.02.017

Pergola, G., Suchan, B., Koch, B., Schwarz, M., Daum, I., and Gunturkun, O. (2013c). Quantitative assessment of chronic thalamic stroke. *AJNR Am. J. Neuroradiol.* 34, E51–E55. doi:10.3174/ajnr.A2897

Pergola, G., Trotta, M., and Suchan, B. (2013d). Asymmetric hemispheric contribution to ERPs in associative memory indexes goal relevance and quantity of information. *Behav. Brain Res.* 241, 7–16. doi:10.1016/j.bbr.2012.11.041

Pergola, G., Gunturkun, O., Koch, B., Schwarz, M., Daum, I., and Suchan, B. (2012). Recall deficits in stroke patients with thalamic lesions covary with damage to the parvocellular mediodorsal nucleus of the thalamus. *Neuropsychologia* 50, 2477–2491. doi:10.1016/j.neuropsychologia.2012.06.019

Peterburs, J., Pergola, G., Koch, B., Schwarz, M., Hoffmann, K. P., Daum, I., et al. (2011). Altered error processing following vascular thalamic damage: evidence from an antisaccade task. *PLoS. ONE* 6:e21517. doi:10.1371/journal.pone.0021517

Peters, J., Daum, I., Gizewski, E., Forsting, M., and Suchan, B. (2009). Associations evoked during memory encoding recruit the context-network. *Hippocampus* 19, 141–151. doi:10.1002/hipo.20490

Peters, J., Koch, B., Schwarz, M., and Daum, I. (2007a). Domain-specific impairment of source memory following a right posterior medial temporal lobe lesion. *Hippocampus* 17, 505–509. doi:10.1002/hipo.20297

Peters, J., Suchan, B., Koster, O., and Daum, I. (2007b). Domain-specific retrieval of source information in the medial temporal lobe. *Eur. J. Neurosci.* 26, 1333–1343. doi:10.1111/j.1460-9568.2007.05752.x

Popken, G. J., Bunney, W. E. Jr., Potkin, S. G., and Jones, E. G. (2000). Subnucleus-specific loss of neurons in medial thalamus of schizophrenics. *Proc. Natl. Acad. Sci. U.S.A.* 97, 9276–9280. doi:10.1073/pnas.150243397

Preuss, T. M., and Goldman-Rakic, P. S. (1987). Crossed corticothalamic and thalamocortical connections of macaque prefrontal cortex. *J. Comp. Neurol.* 257, 269–281. doi:10.1002/cne.902570211

Pustina, D., Gizewski, E., Forsting, M., Daum, I., and Suchan, B. (2012). Human memory manipulated: dissociating factors contributing to MTL activity, an fMRI study. *Behav. Brain Res.* 229, 57–67. doi:10.1016/j.bbr.2011.12.034

Quamme, J. R., Yonelinas, A. P., and Norman, K. A. (2007). Effect of unitization on associative recognition in amnesia. *Hippocampus* 17, 192–200. doi:10.1002/hipo.20257

Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* 98, 676–682. doi:10.1073/pnas.98.2.676

Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus* 20, 1263–1290. doi:10.1002/hipo.20852

Ranganath, C., Johnson, M. K., and D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J. Neurosci.* 20, RC108.

Ranganath, C., Yonelinas, A. P., Cohen, M. X., Dy, C. J., Tom, S. M., and D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia* 42, 2–13. doi:10.1016/j.neuropsychologia.2003.07.006

Ray, J. P., and Price, J. L. (1993). The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J. Comp. Neurol.* 337, 1–31. doi:10.1002/cne.903370102

Reas, E. T., and Brewer, J. B. (2013). Retrieval search and strength evoke dissociable brain activity during episodic memory recall. *J. Cogn. Neurosci.* 25, 219–233. doi:10.1162/jocn_a_00335

Reed, L. J., Lasserson, D., Marsden, P., Stanhope, N., Stevens, T., Bello, F., et al. (2003). FDG-PET findings in the Wernicke-Korsakoff syndrome. *Cortex* 39, 1027–1045. doi:10.1016/S0010-9452(08)70876-1

Reilly, M., Connolly, S., Stack, J., Martin, E. A., and Hutchinson, M. (1992). Bilateral paramedian thalamic infarction: a distinct but poorly recognized stroke syndrome. *Q. J. Med.* 82, 63–70.

Rieck, R. W., Ansari, M. S., Whetsell, W. O. Jr., Deutch, A. Y., and Kessler, R. M. (2004). Distribution of dopamine D2-like receptors in the human thalamus: autoradiographic and PET studies. *Neuropsychopharmacology* 29, 362–372. doi:10.1038/sj.npp.1300336

Rudebeck, S. R., Scholz, J., Millington, R., Rohenkohl, G., Johansen-Berg, H., and Lee, A. C. (2009). Fornix microstructure correlates with recollection but not familiarity memory. *J. Neurosci.* 29, 14987–14992. doi:10.1523/JNEUROSCI.4707-09.2009

Rugg, M. D., and Curran, T. (2007). Event-related potentials and recognition memory. *Trends Cogn. Sci.* 11, 251–257. doi:10.1016/j.tics.2007.04.004

Rugg, M. D., Vilberg, K. L., Mattson, J. T., Yu, S. S., Johnson, J. D., and Suzuki, M. (2012). Item memory, context memory and the hippocampus: fMRI evidence. *Neuropsychologia* 50, 3070–3079. doi:10.1016/j.neuropsychologia.2012.06.004

Russchen, F. T., Amaral, D. G., and Price, J. L. (1987). The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, *Macaca fascicularis*. *J. Comp. Neurol.* 256, 175–210. doi:10.1002/cne.902560202

Sadikot, A. F., Parent, A., and Francois, C. (1992). Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. *J. Comp. Neurol.* 315, 137–159. doi:10.1002/cne.903150203

Salami, M., Itami, C., Tsumoto, T., and Kimura, F. (2003). Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proc. Natl. Acad. Sci. U.S.A.* 100, 6174–6179. doi:10.1073/pnas.0937380100

Saykin, A. J., Gur, R. C., Gur, R. E., Mozley, P. D., Mozley, L. H., Resnick, S. M., et al. (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Arch. Gen. Psychiatry* 48, 618–624. doi:10.1001/archpsyc.1991.01810310036007

Schmahmann, J. D. (2003). Vascular syndromes of the thalamus. *Stroke* 34, 2264–2278. doi:10.1161/01.STR.0000087786.38997.9E

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21. doi:10.1136/jnnp.20.1.11

Segal, J. B., Williams, R., Kraut, M. A., and Hart, J. Jr. (2003). Semantic memory deficit with a left thalamic infarct. *Neurology* 61, 252–254. doi:10.1212/01.WNL.0000073145.08816.E2

Shapira-Lichter, I., Oren, N., Jacob, Y., Gruberger, M., and Hendler, T. (2013). Portraying the unique contribution of the default mode network to internally driven mnemonic processes. *Proc. Natl. Acad. Sci. U.S.A.* 110, 4950–4955. doi:10.1073/pnas.1209888110

Sherman, S. M. (2007). The thalamus is more than just a relay. *Curr. Opin. Neurobiol.* 17, 417–422. doi:10.1016/j.conb.2007.07.003

Sherman, S. M., and Guillery, R. W. (2002). The role of the thalamus in the flow of information to the cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1695–1708.

Sherman, S. M., and Guillery, R. W. (2011). Distinct functions for direct and transthalamic corticocortical connections. *J. Neurophysiol.* 106, 1068–1077. doi:10.1152/jn.00429.2011

Shimamura, A. P. (1995). Memory and the prefrontal cortex. *Ann. N. Y. Acad. Sci.* 769, 151–159.

Shuren, J. E., Jacobs, D. H., and Heilman, K. M. (1997). Diencephalic temporal order amnesia. *J. Neurol. Neurosurg. Psychiatry* 62, 163–168. doi:10.1136/jnnp.62.2.163

Slotnick, S. D. (2013). The nature of recollection in behavior and the brain. *Neuroreport* 24, 663–670. doi:10.1097/WNR.0b013e328362e47e

Smythies, J. (1997). The functional neuroanatomy of awareness: with a focus on the role of various anatomical systems in the control of intermodal attention. *Conscious. Cogn.* 6, 455–481. doi:10.1006/ccog.1997.0315

Soei, E., Koch, B., Schwarz, M., and Daum, I. (2008). Involvement of the human thalamus in relational and non-relational memory. *Eur. J. Neurosci.* 28, 2533–2541. doi:10.1111/j.1460-9568.2008.06536.x

Speedie, L. J., and Heilman, K. M. (1982). Amnestic disturbance following infarction of the left dorsomedial nucleus of the thalamus. *Neuropsychologia* 20, 597–604. doi:10.1016/0028-3932(82)90033-1

Sperling, R. A., Bates, J. F., Chua, E. F., Cocchiarella, A. J., Rentz, D. M., Rosen, B. R., et al. (2003). fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 74, 44–50. doi:10.1136/jnnp.74.1.44

Squire, L. R., and Kandel, E. R. (2000). *Memory: From Mind to Molecules*. Henry: Holt and Company.

Squire, L. R., Wixted, J. T., and Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nat. Rev. Neurosci.* 8, 872–883. doi:10.1038/nrn2154

Staresina, B. P., and Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *J. Neurosci.* 26, 9162–9172. doi:10.1523/JNEUROSCI.2877-06.2006

Stark, C. E., and Okado, Y. (2003). Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *J. Neurosci.* 23, 6748–6753.

Staudigl, T., Zaehle, T., Voges, J., Hanslmayr, S., Esslinger, C., Hinrichs, H., et al. (2012). Memory signals from the thalamus: early thalamocortical phase synchronization entrains gamma oscillations during long-term memory retrieval. *Neuropsychologia* 50, 3519–3527. doi:10.1016/j.neuropsychologia.2012.08.023

Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience* 137, 1087–1106. doi:10.1016/j.neuroscience.2005.10.029

Suchan, B., Gayk, A. E., Schmid, G., Koster, O., and Daum, I. (2008). Hippocampal involvement in recollection but not familiarity across time: a prospective study. *Hippocampus* 18, 92–98. doi:10.1002/hipo.20371

Sziklas, V., and Petrides, M. (1999). The effects of lesions to the anterior thalamic nuclei on object-place associations in rats. *Eur. J. Neurosci.* 11, 559–566. doi:10.1046/j.1460-9568.1999.00448.x

Sziklas, V., and Petrides, M. (2004). Egocentric conditional associative learning: effects of restricted lesions to the hippocampo-mammillo-thalamic pathway. *Hippocampus* 14, 931–934. doi:10.1002/hipo.20044

Taber, K. H., Wen, C., Khan, A., and Hurley, R. A. (2004). The limbic thalamus. *J. Neuropsychiatry Clin. Neurosci.* 16, 127–132. doi:10.1176/appi.neuropsych.16.2.127

Tanji, K., Suzuki, K., Fujii, T., Higano, S., and Yamadori, A. (2003). A case of frontal network amnesia. *J. Neurol. Neurosurg. Psychiatry* 74, 106–109. doi:10.1136/jnnp.74.1.106

Thoma, P., Zoppelt, D., Wiebel, B., and Daum, I. (2006). Recollection and familiarity in negative schizophrenia. *Neuropsychologia* 44, 430–435. doi:10.1016/j.neuropsychologia.2005.05.017

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc. Natl. Acad. Sci. U.S.A.* 94, 14792–14797. doi:10.1073/pnas.94.26.14792

Tsivilis, D., Vann, S. D., Denby, C., Roberts, N., Mayes, A. R., Montaldi, D., et al. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nat. Neurosci.* 11, 834–842. doi:10.1038/nn.2149

Tulving, E. (1987). Multiple memory systems and consciousness. *Hum. Neurobiol.* 6, 67–80.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Tulving, E., and Markowitsch, H. J. (1997). Memory beyond the hippocampus. *Curr. Opin. Neurobiol.* 7, 209–216. doi:10.1016/S0959-4388(97)80009-8

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204. doi:10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.3.CO;2-J

Tunbridge, E. M., Farrell, S. M., Harrison, P. J., and Mackay, C. E. (2013). Catechol-O-methyltransferase (COMT) influences the connectivity of the prefrontal cortex at rest. *Neuroimage* 68, 49–54. doi:10.1016/j.neuroimage.2012.11.059

Uncapher, M. R., Otten, L. J., and Rugg, M. D. (2006). Episodic encoding is more than the sum of its parts: an fMRI investigation of multifeatural contextual encoding. *Neuron* 52, 547–556. doi:10.1016/j.neuron.2006.08.011

Uncapher, M. R., and Rugg, M. D. (2005a). Effects of divided attention on fMRI correlates of memory encoding. *J. Cogn. Neurosci.* 17, 1923–1935. doi:10.1162/089892905775008616

Uncapher, M. R., and Rugg, M. D. (2005b). Encoding and the durability of episodic memory: a functional magnetic resonance imaging study. *J. Neurosci.* 25, 7260–7267. doi:10.1523/JNEUROSCI.1641-05.2005

Van der Werf, Y. D., Jolles, J., Witter, M. P., and Uylings, H. B. (2003a). Contributions of thalamic nuclei to declarative memory functioning. *Cortex* 39, 1047–1062. doi:10.1016/S0010-9452(08)70877-3

Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B., and Jolles, J. (2003b). Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia* 41, 1330–1344. doi:10.1016/S0028-3932(03)00059-9

Van der Werf, Y. D., Witter, M. P., and Groenewegen, H. J. (2002). The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res. Brain Res. Rev.* 39, 107–140. doi:10.1016/S0165-0173(02)00181-9

Vann, S. D. (2010). Re-evaluating the role of the mammillary bodies in memory. *Neuropsychologia* 48, 2316–2327. doi:10.1016/j.neuropsychologia.2009.10.019

Vann, S. D., and Aggleton, J. P. (2004). The mammillary bodies: two memory systems in one? *Nat. Rev. Neurosci.* 5, 35–44. doi:10.1038/nrn1299

Vann, S. D., Aggleton, J. P., and Maguire, E. A. (2009a). What does the retrosplenial cortex do? *Nat. Rev. Neurosci.* 10, 792–802. doi:10.1038/nrn2733

Vann, S. D., Tsivilis, D., Denby, C. E., Quamme, J. R., Yonelinas, A. P., Aggleton, J. P., et al. (2009b). Impaired recollection but spared familiarity in patients with extended hippocampal system damage revealed by 3 convergent methods. *Proc. Natl. Acad. Sci. U.S.A.* 106, 5442–5447. doi:10.1073/pnas.0812097106

Vann, S. D., and Albasser, M. M. (2009). Hippocampal, retrosplenial, and prefrontal hypoactivity in a model of diencephalic amnesia: evidence towards an interdependent subcortical-cortical memory network. *Hippocampus* 19, 1090–1102. doi:10.1002/hipo.20574

Vann, S. D., Saunders, R. C., and Aggleton, J. P. (2007). Distinct, parallel pathways link the medial mammillary bodies to the anterior thalamus in macaque monkeys. *Eur. J. Neurosci.* 26, 1575–1586. doi:10.1111/j.1460-9568.2007.05773.x

Victor, M. A., Adams, R. D., and Collins, G. H. (1989). *The Wernicke-Korsakoff Syndrome and Related Neurologic Disorder Due to Alcoholism and Malnutrition.* Philadelphia, PA: F.A. Davis.

Vilberg, K. L., and Rugg, M. D. (2012). The neural correlates of recollection: transient versus sustained FMRI effects. *J. Neurosci.* 32, 15679–15687. doi:10.1523/JNEUROSCI.3065-12.2012

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., et al. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J. Neurophysiol.* 96, 3517–3531. doi:10.1152/jn.00048.2006

Vogt, B. A., Hof, P. R., Friedman, D. P., Sikes, R. W., and Vogt, L. J. (2008). Norepinephrinergic afferents and cytology of the macaque monkey midline, mediodorsal, and intralaminar thalamic nuclei. *Brain Struct. Funct.* 212, 465–479. doi:10.1007/s00429-008-0178-0

von Cramon, D. Y., Hebel, N., and Schuri, U. (1985). A contribution to the anatomical basis of thalamic amnesia. *Brain* 108(Pt 4), 993–1008. doi:10.1093/brain/108.4.993

von Zerssen, G. C., Mecklinger, A., Opitz, B., and von Cramon, D. Y. (2001). Conscious recollection and illusory recognition: an event-related fMRI study. *Eur. J. Neurosci.* 13, 2148–2156. doi:10.1046/j.0953-816x.2001.01589.x

Voss, J. L., and Paller, K. A. (2010). Bridging divergent neural models of recognition memory: introduction to the special issue and commentary on key issues. *Hippocampus* 20, 1171–1177. doi:10.1002/hipo.20851

Wagner, A. D., Shannon, B. J., Kahn, I., and Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn. Sci.* 9, 445–453. doi:10.1016/j.tics.2005.07.001

Wang, X. J., and Rinzel, J. (1993). Spindle rhythmicity in the reticularis thalami nucleus: synchronization among mutually inhibitory neurons. *Neuroscience* 53, 899–904. doi:10.1016/0306-4522(93)90474-T

Weiler, J. A., Suchan, B., and Daum, I. (2010a). Foreseeing the future: occurrence probability of imagined future events modulates hippocampal activation. *Hippocampus* 20, 685–690. doi:10.1002/hipo.20695

Weiler, J. A., Suchan, B., and Daum, I. (2010b). When the future becomes the past: differences in brain activation patterns for episodic memory and episodic future thinking. *Behav. Brain Res.* 212, 196–203. doi:10.1016/j.bbr.2010.04.013

Weiler, J. A., Suchan, B., Koch, B., Schwartz, M. F., and Daum, I. (2010c). Differential impairment of remembering the past and imagining novel events after thalamic lesions. *J. Cogn. Neurosci.* 23, 3037–3051. doi:10.1162/jocn.2011.21633

Weinberger, D. R., and Harrison, P. J. (2011). *Schizophrenia.* Chichester: Wiley-Blackwell.

Wheeler, M. A., Stuss, D. T., and Tulving, E. (1995). Frontal lobe damage produces episodic memory impairment. *J. Int. Neuropsychol. Soc.* 1, 525–536. doi:10.1017/S1355617700000655

Wiggs, C. L., Weisberg, J., and Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia* 37, 103–118. doi:10.1016/S0028-3932(98)00044-X

Winocur, G., Oxbury, S., Roberts, R., Agnetti, V., and Davis, C. (1984). Amnesia in a patient with bilateral lesions to the thalamus. *Neuropsychologia* 22, 123–143. doi:10.1016/0028-3932(84)90056-3

Witter, M. P., Wouterlood, F. G., Naber, P. A., and Van Haeften, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. *Ann. N. Y. Acad. Sci.* 911, 1–24. doi:10.1111/j.1749-6632.2000.tb06716.x

Wixted, J. T. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychol. Rev.* 114, 152–176. doi:10.1037/0033-295X.114.1.152

Wixted, J. T., Mickes, L., and Squire, L. R. (2010). Measuring recollection and familiarity in the medial temporal lobe. *Hippocampus* 20, 1195–1205. doi:10.1002/hipo.20854

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517. doi:10.1006/jmla.2002.2864

Yonelinas, A. P., Aly, M., Wang, W. C., and Koen, J. D. (2010). Recollection and familiarity: examining controversial assumptions and new directions. *Hippocampus* 20, 1178–1194. doi:10.1002/hipo.20864

Yonelinas, A. P., Kroll, N. E., Dobbins, I., Lazzara, M., and Knight, R. T. (1998). Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation, and receiver operating characteristic data. *Neuropsychology* 12, 323–339. doi:10.1037/0894-4105.12.3.323

Young, K. A., Manaye, K. F., Liang, C., Hicks, P. B., and German, D. C. (2000). Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biol. Psychiatry* 47, 944–953. doi:10.1016/S0006-3223(00)00826-X

Zikopoulos, B., and Barbas, H. (2006). Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J. Neurosci.* 26, 7348–7361. doi:10.1523/JNEUROSCI.5511-05.2006

Zikopoulos, B., and Barbas, H. (2012). Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *J. Neurosci.* 32, 5338–5350. doi:10.1523/JNEUROSCI.4793-11.2012

Zola-Morgan, S., Squire, L. R., and Mishkin, M. (1982). The neuroanatomy of amnesia: amygdala-hippocampus versus temporal stem. *Science* 218, 1337–1339. doi:10.1126/science.6890713

Zoppelt, D., Koch, B., Schwarz, M., and Daum, I. (2003). Involvement of the mediodorsal thalamic nucleus in mediating recollection and familiarity. *Neuropsychologia* 41, 1160–1170. doi:10.1016/S0028-3932(03)00019-8

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Orbitofrontal reality filtering

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Decades of research have deepened our understanding of how the brain forms memories and uses them to build our mental past and future. But how does it determine whether an evoked memory refers to the present and can be acted upon? The study of patients who confuse reality, as evident from confabulation and disorientation, has opened ways to explore this vital capacity. Results indicate that the brain recurs to a phylogenetically old faculty of the orbitofrontal cortex – extinction – and structures of the reward system to keep thought and behavior in phase with reality.

Keywords: orbitofrontal cortex, confabulations, reward system, reality monitoring, continuous recognition

INTRODUCTION

Since the early studies of patients who lost the ability to acquire new memories after damage to the hippocampal area (Scoville and Milner, 1957), the understanding of brain processes allowing the storage of information has been immensely refined (Squire and Wixted, 2011). Memories eventually become independent of the hippocampus, are stored and processed in distributed cortical areas (Squire and Wixted, 2011). Forging plans for the future appears to involve very much the same neural structures that are necessary to store information; building a mental future is very similar to constructing a personal past (Schacter et al., 2007). This raises the question of this review: how does the brain determine whether an upcoming thought pertains to "now"? How do we sense what our current duties are, what day it is, and what ideas we may currently act upon?

LOST SENSE OF REALITY

Brain damage may deprive humans of the ability to sense where they are and what their role is, while leaving other mental capacities intact. Hospitalized patients insisting on their obligation to organize a funeral or to resume military duties were already documented a century ago (Korsakoff, 1891; Kalberlah, 1904). A patient of ours, a retired psychiatrist hospitalized after rupture of aneurysm of the anterior communicating artery, was convinced that she was actually working as a psychiatrist at our clinic and repeatedly left therapy sessions in the conviction that she had to see patients (Schnider et al., 2005a; Schnider, 2008). A young lawyer, suffering from limbic encephalitis, desperately searched for her files, convinced that she was expected at court (Nahum et al., 2010). Both insisted on their resented reality although the hospital environment and therapy sessions should have indicated to them that they were not at work and that their ideas were wrong.

These patients had typical behaviorally spontaneous confabulation (Schnider, 2008), a syndrome first described by Korsakoff (1891) more than 100 years ago: the patients act according to false ideas that can mostly be traced back to real experiences (mostly habits), justify their actions with apparently invented stories (confabulations), are amnesic, and are disoriented regarding time, place, and their current situation.

The disorder was initially described in alcoholic, malnourished people suffering from the Wernicke–Korsakoff syndrome and in subjects having traumatic brain injury (Korsakoff, 1891; Bonhoeffer, 1901; Kalberlah, 1904). Nowadays, it is most frequently reported after rupture of an aneurysm of the anterior communicating artery, traumatic brain injury, or encephalitis (Schnider, 2008). The critical variable is not the type of brain damage, but the location: all hitherto described patients with circumscribed lesions – apart from dementia or a confusional state – had damage to the posterior medial orbitofrontal cortex or of brain regions directly connected with it (**Figure 1**) (Schnider et al., 1996b; Schnider and Ptak, 1999; Gilboa and Moscovitch, 2002; Schnider, 2008). Posterior lesion extension determines how much information the patients can store but is irrelevant for reality confusion as described above (Schnider, 2008). Hippocampal damage is often absent but may also be maximal (Schnider and Ptak, 1999; Nahum et al., 2010). Extremely severe amnesia and extended hippocampal damage do not protect against confabulation, as recently claimed (Dalla Barba and La Corte, 2013).

LIMBIC CONTROL OF MEMORY AND REALITY

These clinical observations alone reveal a fundamental organizing principle of the limbic system's contribution to memory control: while the posterior limbic system with the hippocampus is necessary for long-term encoding of memories (Squire et al., 2004), possibly also the retrieval of episodic details (Moscovitch et al., 2005), the anterior limbic system with the posterior medial orbitofrontal cortex is critical for the sense of whether an activated memory relates to the "now" or not. It signals when an activated memory does not pertain to ongoing reality (Schnider, 2008). It thus prevents behavior from being based on fantasies, that is, ideas that do not refer to the present.

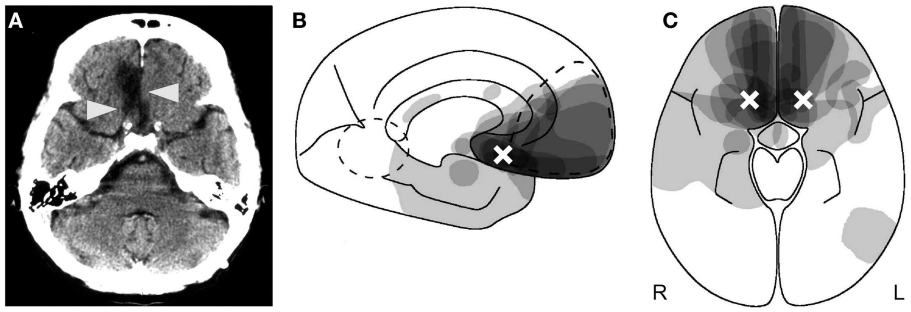


FIGURE 1 | Anatomy of reality filtering. **(A)** Typical orbitofrontal lesion causing reality confusion. In this case, the right gyrus rectus is destroyed (arrowheads) following rupture of an aneurysm of the anterior communicating artery. **(B,C)** Superimposition of the lesions of 14 patients who confused reality for weeks to months. **(B)** Sagittal cut; **(C)** axial cut. As indicated by the shades of gray, maximal lesion overlap was in the posterior medial orbitofrontal area. The white crosses indicate the area of peak activity in healthy subjects who performed a similar task as the one on which the reality-confusing patients failed. **(B,C)** Reproduced from Schnider (2008), with permission.

SENSE OF TIME

Reality-confusing patients also have a disturbed sense for the "now," the "perceived or psychological present," defined as the duration of an experiential process, suggested to take about 0.1–5 s (Fraisse, 1984). In comparison to non-confabulating amnesics and healthy controls, reality-confusing patients failed to discriminate short, temporally overlapping intervals in the range of 0.2–3 s (Schnider, 2000). Similar findings have been obtained in patients with damage of the basal ganglia or cerebellum (Ivry and Keele, 1989; Gibbon et al., 1997; Riesen and Schnider, 2001). These structures were also activated, together with dorsolateral prefrontal and parietal cortex, in functional magnetic resonance imaging (fMRI) of time estimation and reproduction (Bueti et al., 2008). Damage to these structures does not induce reality confusion. It might, therefore, be that the disturbed discrimination within the psychological present in reality-confusing patients either reflects an independent time function, not causally related to reality confusion, or that the posterior medial orbitofrontal cortex, which is difficult to discern in fMRI due to artifacts, holds a central role in the sense of the "now," but requires participation of association areas. The precise significance of the finding is as yet unclear.

EXPLORING THE SENSE OF REALITY

In any case, the temporal difficulty of reality-confusing patients transcends the perception of the present moment: they apparently fail to place themselves correctly in time and space. They act as obstinately on ideas that have no relation with the present as on ideas that refer to the present. How might one experimentally seize this intrusion of thoughts, which have no relation with the present, into their concept of reality and actions? We were lucky to develop a task, which tests the sense for memories' relation with the "now" and which has proved very reliable in separating reality-confusing patients from other amnesic subjects (Schnider et al., 1996a; Schnider and Ptak, 1999; Nahum et al., 2012). The task uses repeated runs of a continuous recognition test, in which subjects see a long series of pictures and have to indicate picture recurrences within the ongoing run (**Figure 2**). When subjects do such a task for the first time, they can recognize picture repetitions on the sole basis of familiarity (**Figure 2A**). Healthy subjects performing such a first run activated the hippocampal area (Schnider et al., 2000b).

As subjects repeat the task, always composed of the same picture series, familiarity alone is not sufficient anymore; all items look familiar. Thus, the recognition of a repetition within the ongoing run now requires the ability to sense whether a picture was previously seen within the ongoing run (the "present reality" of the ongoing run) or a previous run; it requires reality filtering (**Figure 2B**). Despite this requirement, healthy subjects perform the task intuitively, with no particular effort: reaction times are similar to the first run and errors (false positive responses) are very scarce (Schnider et al., 2002; Wahlen et al., 2011). Indeed, it has proved very difficult to develop a task version which lowered performance of healthy subjects (Schnider et al., 2010).

When healthy subjects performed repeated runs of this task, they had activation of the posterior medial orbitofrontal cortex, area 13 (**Figures 1B,C**) (Schnider et al., 2000b), which corresponds to the area of maximal damage in patients who confuse reality.

The task structurally resembles well-known source memory tasks requiring attribution of stimuli to previous task stages, such as, the exclusion condition of the process dissociation procedure (Jacoby, 1991), in that it has multiple runs. Despite this resemblance, the processes involved in such tasks are very different from ours: they require conscious, effortful monitoring (Jacoby, 1991), activate the dorsolateral prefrontal (rather than orbitofrontal) cortex (Rugg et al., 2003), and have no predictive value for the occurrence of behaviorally spontaneous confabulation (Johnson et al., 1997). Reality filtering is not about knowing to what episode in the past a memory refers but whether it pertains to present reality or not.

Our reality-filtering task, as easy as it may be for healthy subjects, proved an insurmountable challenge for reality-confusing patients, even at much longer intervals between the runs (30–60 min) than in healthy subjects (1 min). While healthy subjects and non-confabulating amnesics maintained performance over repeated runs, reality-confusing patients had a sharp increase of false positive responses: they believed increasingly more often that they had already seen pictures within the ongoing run, which in

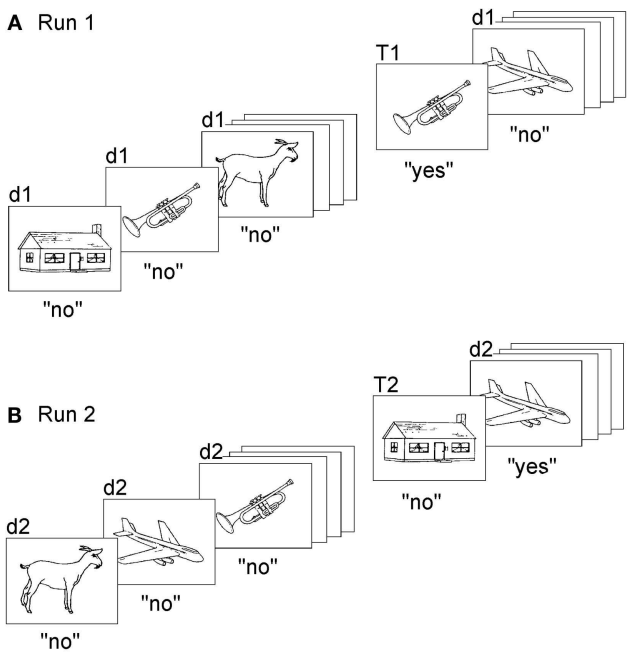


FIGURE 2 | Task to measure the sense of present reality. Subjects make two runs (or more) of a continuous recognition task, each run composed of the same set of pictures. Subjects have to indicate, in both runs, only repetitions within the ongoing run (original version: Schnider et al., 1996a). **(A)** The first run demands learning and recognition and can be solved on the basis of familiarity alone. **(B)** In the second run, all items are already familiar. The task now demands the ability to distinguish between memories that pertain to the ongoing run (repetitions within the run, T2) and memories that do not (d2; not previously presented within the run, albeit familiar from the first run). Confabulating patients had a steep increase of false positives in response to d2 stimuli. "d" denotes "distracters," i.e., pictures' first appearance within a run; "T" denotes targets, i.e., repeated pictures within the run. "d1" and "T1" are stimuli presented in the first run, "d2" and "T2" are stimuli of the second run. "Yes" and "no" indicate correct responses. Illustration reproduced from Schnider (2008), with permission.

reality appeared for the first time within the run (Schnider et al., 1996a; Schnider and Ptak, 1999; Nahum et al., 2012). This increase of false positives was also tightly associated with the degree of disorientation, that is, the number of false answers to questions about current time, place, or situation (Schnider et al., 1996b; Nahum et al., 2012). Recovery of the ability to sense that familiar items had not yet appeared within the ongoing run was individually predictive of the recovery of the sense of reality with cessation of confabulations and inappropriate acts and re-installment of correct orientation (Schnider et al., 2000a). The increase of false positives in reality-confusing patients indicates that orbitofrontal reality-filtering functions by exclusion: it signals when a memory does not relate to current reality.

PRECONSCIOUS REALITY FILTERING

The conviction that healthy subjects, but also reality-confusing patients hold in their concept of current reality – the present day, their current role and location, etc. – suggests that reality filtering is an early process, which precedes conscious control. Experimental evidence supports this notion. When healthy subjects performed a similar task while their brain activity was observed with electroencephalography, processing of new and repeated items in the first run, which requires learning and recognition, differed over posterior electrodes at around 400–600 ms (Schnider et al., 2002; Wahlen et al., 2011). By contrast, processing of new items in the second run, which requires reality filtering, induced a strikingly different electrocortical potential than all other stimuli of the first and second run: at 200–300 ms, they did not evoke a negative frontal potential common to all other stimuli. Thus, correct processing of the stimuli on which reality-confusing patients had failed (first presentations within the second run) differed from all other stimuli at an early stage, before processes of recognition set in. In other words, even before we recognize the precise content of an upcoming memory (thought), the orbitofrontal cortex has already decided whether it refers to ongoing reality or not.

Spatio-temporal analysis of the electrical activity over the whole brain indicated that the absence of the negative potential reflected the fact that new stimuli of the second run skipped a processing stage common to all other stimuli, which was characterized by a particularly extended neocortical, temporo-parietal area of synchronous activity (Schnider et al., 2002; Schnider, 2003; Wahlen et al., 2011), as indicated by source estimation (Michel et al., 2004). This suggests that, whenever a memory is activated that does not relate to reality (fantasy), neocortical synchronization is transiently inhibited at 200–300 ms (Schnider, 2003). Fantasies would thus assume a different electrocortical format than thoughts that pertain to ongoing reality and that have passed through the stage of extended neocortical activation (Schnider, 2008).

This sequence of processes – first reality filtering, then recognition and re-encoding of memories (thoughts), as depicted in **Figure 3A** – not only ensures that we distinguish between memories that pertain to ongoing reality and memories that do not, but also that we know tomorrow whether we have really experienced a situation today or only thought about it; as these thoughts (memories) are re-encoded, they are labeled as referring to reality or as a fantasy (Schnider, 2008). In reality-confusing patients (**Figure 3B**), memories that do not relate to reality are not filtered and thus assume the same format as memories relating to reality. Any upcoming thought, be it a memory of the past, a thought about the present, or a plan for the future, is sensed as if it referred to the present. Depending on the evoked memories, patients' behavior sometimes agrees, sometimes disagrees with reality. As far as the patients encode their own thoughts, they experience them as if they referred to reality and may, therefore, subsequently produce false statements about the past, present, or future. In agreement with this interpretation, confabulating patients may recall events that they have simply talked about, as if they had really experienced them (Schnider et al., 2005a).

Reality filtering is not limited to visual information: we observed similar orbitofrontal activation in functional imaging with visually presented verbal or non-verbal visual material (Treyer et al., 2003) as well as with auditorily presented words (Treyer et al., 2006). The process is precise: the electrocortical signal was much more distinct when stimuli between the runs were identical with, rather than only resembled previously presented ones (Wahlen et al., 2011). Thus, reality filtering seems to be challenged particularly when present reality is very similar to a past reality.

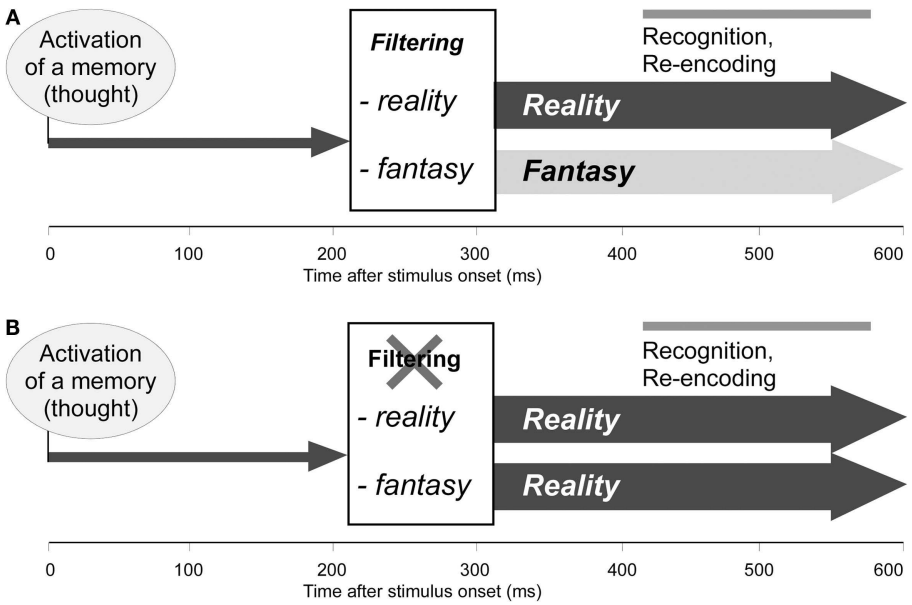


FIGURE 3 | Functional model of the orbitofrontal reality filter. **(A)** Normal function: 200–300 ms after activation of a memory (thought), reality filtering sets in, inhibiting extended neocortical activation when the upcoming memory does not relate to ongoing reality. At 400–600 ms, the activated memory (thought) is recognized and again encoded (Schnider et al., 2002; Wahlen et al., 2011). **(B)** Hypothetical dysfunction of reality filtering in reality-confusing patients: memories (thoughts) are normally activated, but are not checked regarding their relation with reality; all memories are activated, and later recognized and re-encoded, as if they related to ongoing reality. Adapted from Schnider (2008), with permission.

Finally, the process is distinct from other memory control mechanisms: to recognize that a stimulus only resembles, but is not identical with a previously seen stimulus (task described by Gilboa et al., 2006) also evokes an electrocortical signal at 200–300 ms but with inverse polarity than the one produced by reality filtering (Wahlen et al., 2011). That is, the recognition of a memory's concordance with the present (reality filtering) dissociates from the recognition of its concordance with the past (its content).

ORBITOFRONTAL CORTEX AND REALITY FILTERING

The posterior medial orbitofrontal cortex is a phylogenetically old and ontogenetically consistent structure (Chiavaras et al., 2001). One may, therefore, wonder what specific faculty enables it to assume the role of a reality filter. Reality-confusing patients fail to adapt to the fact that their anticipations never come true: the hospitalized psychiatrist did not find her expected patients, the lawyer did not find the colleagues and judges she expected to meet. Yet, both continued to act according to such anticipations – based on habits – as if they were still valid. This behavior is reminiscent of animals continuing to choose a conditioned stimulus, which was previously followed by reward, even after this association has proved to be no longer valid. The ability to learn from the fact that a stimulus is no longer followed by reward and to abandon a previously valid stimulus-outcome association is called extinction (Pavlov, 1927; Ouyang and Thomas, 2005). In non-human primates, lesions of the posterior medial orbitofrontal cortex, corresponding to area 13, induced a specific deficit of extinction, unlike damage to any other region of the prefrontal lobes (Butter, 1969). Single cell recordings showed that this area contains a particularly high density of neurons that specifically discharge when an expected reward fails to be delivered (Rosenkilde et al., 1981). Our hypothesis is that the brain uses this neural signal to label an upcoming memory as not pertaining to ongoing reality, that is, as a fantasy. The neurons producing this signal might be appropriately described as "reality neurons."

Clinical evidence supports this hypothesis: we asked a group of amnesic subjects to perform a reversal learning task, in which they had to predict which one of two faces would have a target stimulus on the nose (Nahum et al., 2009). Reality-confusing patients did not differ from other amnesics in their ability to learn the association, but they had significantly more difficulty in switching to the alternate face after trials indicating absence of the target stimulus. Over all patients, this difficulty, but not other cognitive measures, highly correlated with the degree of disorientation.

The data indicate that, rather than invoking high-level monitoring mechanisms, the brain uses a phylogenetically old capacity, already available to primitive creatures like aplysia (Hawkins et al., 2006) and drosophila (Schwaerzel et al., 2002), to keep thought and behavior in phase with reality: it uses the neural signal that also underlies behavioral extinction. So, evolution did not have to devise a separate mechanism to assure the behaviorally appropriate use of an ever-increasing stock of memories in higher species like humans.

REALITY CHECK AND REWARD SYSTEM

These results point to a hitherto unappreciated role of the orbitofrontal cortex and the reward system in reality filtering beyond processing the pleasure associated with outcomes. Indeed,

orbitofrontal activity does not depend on the prospect of pleasure: the human orbitofrontal cortex is also activated when anticipating and monitoring neutral events devoid of any tangible reward value (Schnider et al., 2005b). In such a task, the non-occurrence of anticipated outcomes induced a distinct electrocortical signal, which occurred in the same period (200–300 ms) and with a similar configuration (frontal positivity) as the signal produced in reality filtering (Schnider et al., 2007). Indeed, it appears that, in humans, posterior orbitofrontal activity in response to the non-delivery of expected reward is driven much more by the need to adapt behavior than the sole absence of the reward; when there was no need to adapt behavior, absence of reward did not activate this area (Nahum et al., 2011). While these results do not question the role of the orbitofrontal cortex in hedonic processing (Kringelbach, 2005), decision-making, and optimizing behavior (Bechara et al., 1997; Wallis, 2007), they underscore that the orbitofrontal cortex contains the neural apparatus allowing it to function as a generic reality-filtering system, irrespective of whether reward is at stake or not.

The similarity between reality filtering and reward processing extends to transmitter systems. While select orbitofrontal neurons increase firing when an anticipated reward fails to occur (Rosenkilde et al., 1981; Thorpe et al., 1983), dopaminergic neurons in the nigro-striatal system transiently decrease their firing (Schultz et al., 1997; Schultz, 2007). A "hyper-dopaminergic" state would, accordingly, be expected to impair reality filtering. This is what we found (Schnider et al., 2010): when healthy subjects performed a very difficult version of our reality-filtering task under the influence of L-DOPA, which is transformed to dopamine in the brain, they produced specifically more false positive responses than when they received a dopamine antagonist (risperidone). Thus, reality filtering, similar to reward processing, is under dopaminergic modulation. Of note, a hyper-dopaminergic state has also been suspected to underlie schizophrenia, another disorder characterized by reality confusion (Howes and Kapur, 2009). Actively hallucinating schizophrenic patients failed in our reality-filtering task (Badcock et al., 2005). Pervasive confabulations were described in such patients in the nineteenth century (Kraepelin, 1887/88) before the advent of neuroleptics (dopamine antagonists) in the late 1940s. The implication of diverse dopamine sub-systems and other transmitter systems in reward and outcome processing is a topic of current research (Schultz and Dickinson, 2000; Bromberg-Martin et al., 2010); their role for reality filtering is entirely unknown.

Available data suggest a link between orbitofrontal activity and subcortical dopaminergic transmission. The orbitofrontal cortex projects onto dopaminergic neurons in the midbrain (Joel and Weiner, 2000), which, in turn, project onto, and modulate activity in frontal-subcortical loops that connect specific areas of the prefrontal lobes, including the orbitofrontal cortex, with themselves and other frontal areas (Alexander et al., 1986). By transiently inhibiting dopaminergic neurons, the orbitofrontal cortex might thus modulate activity in subcortical connections and convey the signal inhibiting neocortical synchronization when an upcoming memory does not relate to reality. In agreement with this, we observed activation of a loop connecting the orbitofrontal cortex with the striatum, substantia nigra, and the medial thalamus when healthy subjects performed a more sensitive version of the reality-filtering task containing different stimulus types (Treyer et al., 2003). This result, together with the pharmacological evidence, suggests that reality filtering not only relies on the same orbitofrontal signal, but also on the same circuitry as the one used to signal that an anticipated reward failed to occur. We surmise that reality filtering is a specific instance of "reward" processing: it refers to all types of outcomes, irrespective of hedonic value, and specifically processes the situation that anticipated events fail to happen.

COMPARISON WITH OTHER HYPOTHESES

Orbitofrontal reality filtering, as described in this review, does not yet have the status of a distinct, acknowledged brain function. Accordingly, there is no hypothesis to compare it with. By contrast, the two obvious disorders resulting from its dysfunction – disorientation and confabulation – have received the attention of cognitive models.

Disorientation has been linked to amnesia and perception: an uninterrupted flow of memories and correct perception of the environment would be necessary to maintain orientation in time and space (Kraepelin, 1909; Benton et al., 1964; High et al., 1990). Our data only partially support this notion: the severity of amnesia, as measured with a continuous recognition task, is only weakly associated with disorientation (Schnider et al., 1996b; Schnider, 2008). However, early authors also speculated that there might be a distinct function of orientation (Bleuler, 1923) and Jaspers (1973) separated "delusional disorientation" in patients with full consciousness as a distinct form. Deficient reality filtering might be the mechanism they thought of.

Confabulations have been the topic of diverse hypotheses. Most of them tried to explain confabulations as a verbal phenomenon, irrespective of inappropriate behavior or disorientation. The question at the center of these hypotheses was: "What makes patients tell incorrect stories and fabricate false responses to questions?" The question at the basis of our studies was: "why do the patients confuse reality?"

The first question refers to two forms of confabulation: (1) Intrusions in memory tests (simple provoked confabulations). These dissociate from all other forms of confabulation and are independent of reality confusion (Schnider et al., 1996a; Nahum et al., 2012). (2) Momentary confabulations (also called out-of-embarrassment confabulations) (Bonhoeffer, 1901; Van der Horst, 1932; Schnider, 2008) that patients produce in discussions or in response to questions. It is the most commonly reported form of confabulation. It need not be accompanied by disorientation. Only a relatively small proportion of patients who produce momentary confabulations have deficient reality filtering (Nahum et al., 2012).

The second question refers to two other forms: (3) behaviorally spontaneous confabulation, as defined above – the topic of this review. It can be conceived as a specific subform of momentary confabulations, namely, the form caused by reality confusion, as evident from inappropriate acts in accordance with the confabulations and disorientation. (4) Fantastic confabulations, which defy any sense of plausibility. These are rare and occur in severe confusion, dementia, or psychosis (Schnider, 2008).

Most hypotheses did not distinguish between forms of confabulations. Thus, they have differing significance for the explanation of behaviorally spontaneous confabulation and reality confusion. The most prominent hypotheses can be summarized as follows: (1) Confabulations emanate from a combination of amnesia with frontal executive failures. The hypothesis stems from the observation that executive functions may recover in parallel with the cessation of confabulations (Papagno and Baddeley, 1997; Nys et al., 2004) and that confabulations in cohorts of brain damaged patients are associated with executive dysfunction (Cunningham et al., 1997). However, patients with behaviorally spontaneous confabulation did not differ from similarly severe non-confabulating amnesics with regards to executive functions (Schnider et al., 1996a; Schnider and Ptak, 1999; Nahum et al., 2012). (2) Confabulations reflect a desire to fill gaps in memory or may compensate for the embarrassment of being unable to respond to questions (Flament, 1957; Conway and Tacci, 1996; Fotopoulou et al., 2008). This mechanism appears to account for a certain proportion of momentary confabulations, but was not associated with behaviorally spontaneous confabulation or disorientation (Schnider et al., 1996a; Nahum et al., 2012). Nonetheless, it may be that this mechanism explains the content of false ideas, possibly also the tendency to talk about them. If reality filtering fails, then patients not only talk about, but also act in accordance with these ideas. (3) Confabulations emanate from deficient monitoring of the source (spatial, temporal, personal context) of memories (Johnson and Raye, 1998). Insofar as this function has been defined by experimental procedures, which typically require effortful and conscious monitoring (see process dissociation procedure, above), it has failed to differentiate confabulating from non-confabulating patients (own unpublished data and Johnson et al., 1997). Conversely, reality filtering, which precedes the re-encoding of thoughts, is likely to be a prerequisite for later source monitoring. (4) Confabulations reflect insufficient monitoring of memories' content (Moscovitch and Melo, 1997; Gilboa et al., 2006). Confabulating patients who failed both in our reality-filtering task and a task requiring fine distinction between closely similar items were indeed described (Gilboa et al., 2006). We found that these two challenges evoked different cortical processes (Wahlen et al., 2011). It may be that in select patient groups, both processes may contribute to the occurrence and the content of confabulations. (5) Confabulations results from a deficient temporal tag of memories or reflect temporally displaced consciousness (Van der Horst, 1932; Talland, 1961; Dalla Barba, 2002; Dalla Barba and La Corte, 2013). The hypothesis is based on the observation that confabulations very often are rooted in patients' true experiences and falsely recombine elements of real events. While these authors never proposed a way to experimentally verify the hypothesis, the idea is entirely compatible with the concept of reality filtering, but with a twist: reality filtering only explains confabulations emanating from reality confusion and, therefore, only a certain proportion of confabulations.

LIMITATIONS OF THE TASK

The continuous recognition task used to test reality filtering, as predictive as it has been in clinical practice and as consistent imaging and electrophysiological results have been, has its limitations. First, it may fail to seize memory confusion in patients with extremely severe amnesia who fail to encode any information in the first run (Schnider et al., 1996a). Such patients still failed in the extinction task (Nahum et al., 2009; Schnider et al., 2013). Second, like any cognitive test, a subject's strategy may influence results. One of our patients was so skeptical about the difficulties of the second run that he rejected all items as being repetitions. When the task was repeated indicating that not only his correct rejections, but also his correct recognitions would be counted, the typical pattern of memory confusion became apparent (Ptak and Schnider, 1999). Third, in our studies, patients were matched according to the severity of amnesia. There are indications that, if patients are selected according to a single etiology, irrespective of the severity of cognitive deficits, the task may not be very predictive of reality confusion (Joray et al., 2004; Gilboa et al., 2006). Fourth, the most important limitation of the task is its specificity. As this review should make clear, it has been developed to measure reality confusion; it is not a predictor of all forms of confabulation. This limitation, of course, applies to the whole concept of orbitofrontal reality filtering.

PERSPECTIVES

A number of questions remain: what qualifies a real-world memory, composed of different modalities, as pertaining to reality? Is there a hierarchy of modalities, for example, with visual information, which is used in most experiments, prevailing over tactile information? Then, there are anatomical enigmas: first, virtually all patients confusing reality after an orbitofrontal lesion eventually regain the sense of reality, albeit sometimes only after many months (Schnider et al., 2000a, 2005a). This suggests that the neural apparatus ensuring reality filtering – presumably the outcome monitoring system – is redundantly organized or may undergo plastic changes after damage, similar to other systems. What brain areas and mechanism allow these patients to regain the sense of reality? Secondly, only a minority of people having a classic disease and orbitofrontal lesion actually suffer sustained reality confusion (Schnider, 2008); a typical lesion alone does not reliably predict the occurrence of reality confusion. Thus, do reality-confusing patients have the misfortune of concentrating their reality cells in the areas damaged by the common causes of behaviorally spontaneous confabulation? Is there a genetic predisposition for such an arrangement or for the ability to rapidly adapt thought to ongoing reality?

While some of these questions can be examined in humans, others need the precision of animal experimentation. The association between human reality filtering and the capacity to abandon previously valid anticipations suggests that extinction trials in reward tasks would be an appropriate animal model of human reality filtering. In contrast to extinction of fear memories (in which the animals gain access to a previously avoided stimulus) (LeDoux, 1996; Quirk et al., 2010) extinction of reward associations (in which the animals give up a previously rewarding association) has rarely been studied because such trials rapidly discourage the animals from participating. Experimentation would

thus take longer. The investment may clearly be worth it: a better understanding of the processes underlying reality filtering might open new ways to treat diseases impairing the sense of reality.

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REFERENCES

Alexander, G. E., Delong, M. R., and Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381. doi:10.1146/annurev.ne.09.030186.002041

Badcock, J. C., Waters, F. A., Maybery, M. T., and Michie, P. T. (2005). Auditory hallucinations: failure to inhibit irrelevant memories. *Cogn. Neuropsychiatry* 10, 125–136. doi:10.1080/13546800344000363

Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science* 275, 1293–1295. doi:10.1126/science.275.5304.1293

Benton, A. L., Van Allen, M. W., and Fogel, M. L. (1964). Temporal orientation in cerebral disease. *J. Nerv. Ment. Dis.* 139, 110–119. doi:10.1097/00005053-196408000-00003

Bleuler, E. (1923). *Lehrbuch der Psychiatrie.* Berlin: Julius Springer Verlag.

Bonhoeffer, K. (1901). *Die Akuten Geisteskrankheiten des Gewohnheitstrinkers. Eine klinische Studie.* Jena: Gustav Fischer.

Bromberg-Martin, E. S., Matsumoto, M., and Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron* 68, 815–834. doi:10.1016/j.neuron.2010.11.022

Bueti, D., Walsh, V., Frith, C., and Rees, G. (2008). Different brain circuits underlie motor and perceptual representations of temporal intervals. *J. Cogn. Neurosci.* 20, 204–214. doi:10.1162/jocn.2008.20017

Butter, C. M. (1969). Perseveration in extinction and in discrimination reversal tasks following selective frontal ablations in *Macaca mulatta*. *Physiol. Behav.* 4, 163–171. doi:10.1016/0031-9384(69)90075-4

Chiavaras, M. M., Legoualher, G., Evans, A., and Petrides, M. (2001). Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. *Neuroimage* 13, 479–496. doi:10.1006/nimg.2000.0641

Conway, M. A., and Tacci, P. C. (1996). Motivated confabulation. *Neurocase* 2, 325–339. doi:10.1093/neucas/2.4.325-a

Cunningham, J. M., Pliskin, N. H., Cassisi, J. E., Tsang, B., and Rao, S. M. (1997). Relationship between confabulation and measures of memory and executive function. *J. Clin. Exp. Neuropsychol.* 19, 867–877. doi:10.1080/01688639708403767

Dalla Barba, G., and La Corte, V. (2013). The hippocampus, a time machine that makes errors. *Trends Cogn. Sci. (Regul. Ed.)* 17, 102–104. doi:10.1016/j.tics.2013.01.005

Dalla Barba, G. F. (2002). *Memory, Consciousness and Temporality*. Boston: Kluwer Academic Publishers.

Flament, J. (1957). La fabulation dans le syndrome de Korsakov d'étiologie traumatique. Considérations cliniques, psycho-pathologiques et neuro-pathologiques à propos d'une observation de fabulation à caractère mythopathique. *Acta Neurol. Belg.* 57, 119–161.

Fotopoulou, A., Conway, M. A., Tyrer, S., Birchall, D., Griffiths, P., and Solms, M. (2008). Is the content of confabulation positive? An experimental study. *Cortex* 44, 764–772. doi:10.1016/j.cortex.2007.03.001

Fraisse, P. (1984). Perception and estimation of time. *Annu. Rev. Psychol.* 35, 1–36. doi:10.1146/annurev.ps.35.020184.000245

Gibbon, J., Malapani, C., Dale, C. L., and Gallistel, C. (1997). Toward a neurobiology of temporal cognition: advances and challenges. *Curr. Opin. Neurobiol.* 7, 170–184. doi:10.1016/S0959-4388(97)80005-0

Gilboa, A., Alain, C., Stuss, D. T., Melo, B., Miller, S., and Moscovitch, M. (2006). Mechanisms of spontaneous confabulations: a strategic retrieval account. *Brain* 129, 1399–1414. doi:10.1093/brain/awl093

Gilboa, A., and Moscovitch, M. (2002). "The cognitive neuroscience of confabulation: a review and a model," in *The Handbook of Memory Disorders*, 2nd Edn, eds A. Baddeley, M. D. Kopelman, and B. Wilson (West Sussex: John Wiley & Sons), 315–342.

Hawkins, R. D., Clark, G. A., and Kandel, E. R. (2006). Operant conditioning of gill withdrawal in Aplysia. *J. Neurosci.* 26, 2443–2448. doi:10.1523/JNEUROSCI.3294-05.2006

High, W. M., Levin, H. S., and Gary, H. E. (1990). Recovery of orientation following closed head injury. *J. Clin. Exp. Neuropsychol.* 12, 703–714. doi:10.1080/01688639008401013

Howes, O. D., and Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III – the final common pathway. *Schizophr. Bull.* 35, 549–562. doi:10.1093/schbul/sbp006

Ivry, R. B., and Keele, S. W. (1989). Timing functions of the cerebellum. *J. Cogn. Neurosci.* 1, 136–152. doi:10.1162/jocn.1989.1.2.136

Jacoby, L. L. (1991). A process dissociation framework: separating automatic from intentional uses of memory. *J. Mem. Lang.* 30, 513–541. doi:10.1016/0749-596X(91)90025-F

Jaspers, K. (1973). *Allgemeine Psychopathologie.* Berlin: Springer-Verlag.

Joel, D., and Weiner, I. (2000). The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96, 451–474. doi:10.1016/S0306-4522(99)00575-8

Johnson, M. K., O'Connor, M., and Cantor, J. (1997). Confabulation, memory deficits, and frontal dysfunction. *Brain Cogn.* 34, 189–206. doi:10.1006/brcg.1997.0873

Johnson, M. K., and Raye, C. L. (1998). False memories and confabulation. *Trends Cogn. Sci. (Regul. Ed.)* 2, 137–145. doi:10.1016/S1364-6613(98)01152-8

Joray, S., Herrmann, F., Mulligan, R., and Schnider, A. (2004). Mechanism of disorientation in Alzheimer's disease. *Eur. Neurol.* 52, 193–197. doi:10.1159/000082034

Kalberlah, F. (1904). Ueber die acute Commotionspsychose, zugleich ein Beitrag zur Aetiologie des Korsakow'schen Symptomenkomplexes. *Arch. Psychiatr. Nervenkr.* 38, 402–438. doi:10.1007/BF02173472

Korsakoff, S. S. (1891). Erinnerungstäuschungen (Pseudoreminiscenzen) bei polyneuritischer Psychose. *Allg. Z. Psychiatr. Psych. Med.* 47, 390–410.

Kraepelin, E. (1909). *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. I. Band, Allgemeine Psychiatrie.* Leipzig: Johann Ambrosius Barth Verlag.

Kraepelin, E. (1887/88). Ueber Erinnerungsfälschungen. *Arch. Psychiatr. Nervenkr.* 17, 830–843. doi:10.1007/BF02207467

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 6, 691–702. doi:10.1038/nrn1747

LeDoux, J. (1996). *The Emotional Brain. The Mysterious Underpinnings of Emotional Life.* New York: Simon & Schuster.

Michel, C. M., Murray, M. M., Lantz, G., Gonzalez, S., Spinelli, L., and Grave De Peralta, R. (2004). EEG source imaging. *Clin. Neurophysiol.* 115, 2195–2222. doi:10.1016/j.clinph.2004.06.001

Moscovitch, M., and Melo, B. (1997). Strategic retrieval and the frontal lobes: evidence from confabulation and amnesia. *Neuropsychologia* 35, 1017–1034. doi:10.1016/S0028-3932(97)00028-6

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., et al. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J. Anat.* 207, 35–66. doi:10.1111/j.1469-7580.2005.00421.x

Nahum, L., Bouzerda-Wahlen, A., Guggisberg, A., Ptak, R., and Schnider, A. (2012). Forms of confabulation: dissociations and associations. *Neuropsychologia* 50, 2524–2534. doi:10.1016/j.neuropsychologia.2012.06.026

Nahum, L., Gabriel, D., and Schnider, A. (2011). Human processing of behaviorally relevant and irrelevant absence of expected rewards: a high-resolution ERP study. *PLoS ONE* 6:e16173. doi:10.1371/journal.pone.0016173

Nahum, L., Ptak, R., Leemann, B., Lalive, P., and Schnider, A. (2010). Behaviorally spontaneous confabulation in limbic encephalitis: the roles of strategic monitoring and reality filtering. *J. Int. Neuropsychol. Soc.* 16, 995–1005. doi:10.1017/S1355617710000780

Nahum, L., Ptak, R., Leemann, B., and Schnider, A. (2009). Disorientation, confabulation, and extinction capacity. Clues on how the brain creates reality. *Biol. Psychiatry* 65, 966–972. doi:10.1016/j.biopsych.2009.01.007

Nys, G. M., Van Zandvoort, M. J., Roks, G., Kappelle, L. J., De Kort, P. L., and De Haan, E. H. (2004). The role of executive functioning in spontaneous confabulation. *Cogn. Behav. Neurol.* 17, 213–218.

Ouyang, M., and Thomas, S. A. (2005). A requirement for memory retrieval during and after long-term extinction learning. *Proc. Natl. Acad. Sci. U.S.A.* 102, 9347–9352. doi:10.1073/pnas.0502315102

Papagno, C., and Baddeley, A. (1997). Confabulation in a dysexecutive patient: implication for models of retrieval. *Cortex* 33, 743–752. doi:10.1016/S0010-9452(08)70731-7

Pavlov, P. I. (1927). *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*, trans. G. V. Anrep (London: Oxford University Press).

Ptak, R., and Schnider, A. (1999). Spontaneous confabulations after orbitofrontal damage: the role of temporal context confusion and self-monitoring. *Neurocase* 5, 243–250. doi:10.1080/1355479990840 2729

Quirk, G. J., Pare, D., Richardson, R., Herry, C., Monfils, M. H., Schiller, D., et al. (2010). Erasing fear memories with extinction training. *J. Neurosci.* 30, 14993–14997. doi:10.1523/JNEUROSCI.4268-10.2010

Riesen, J., and Schnider, A. (2001). Time estimation in Parkinson's disease: normal long term estimation despite impaired short duration discrimination. *J. Neurol.* 248, 27–35. doi:10.1007/s004150170266

Rosenkilde, C. E., Bauer, R. H., and Fuster, J. M. (1981). Single cell activity in ventral prefrontal cortex of behaving monkeys. *Brain Res.* 209, 375–394. doi:10.1016/0006-8993(81)90160-8

Rugg, M. D., Henson, R. N., and Robb, W. G. (2003). Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. *Neuropsychologia* 41, 40–52. doi:10.1016/S0028-3932(02)00129-X

Schacter, D. L., Addis, D. R., and Buckner, R. L. (2007). Remembering the past to imagine the future: the prospective brain. *Nat. Rev. Neurosci.* 8, 657–661. doi:10.1038/nrn2213

Schnider, A. (2000). Spontaneous confabulations, disorientation, and the processing of 'now'. *Neuropsychologia* 38, 175–185. doi:10.1016/S0028-3932(99)00064-0

Schnider, A. (2003). Spontaneous confabulation and the adaptation of thought to ongoing reality. *Nat. Rev. Neurosci.* 4, 662–671. doi:10.1038/nrn1179

Schnider, A. (2008). *The Confabulating Mind. How the Brain Creates Reality*. Oxford: Oxford University Press.

Schnider, A., Bonvallat, J., Emond, H., and Leemann, B. (2005a). Reality confusion in spontaneous confabulation. *Neurology* 65, 1117–1119. doi:10.1212/01.wnl.0000178900.37611.8d

Schnider, A., Treyer, V., and Buck, A. (2005b). The human orbitofrontal cortex monitors outcomes even when no reward is at stake. *Neuropsychologia* 43, 316–323. doi:10.1016/j.neuropsychologia.2004.07.003

Schnider, A., Guggisberg, A., Nahum, L., Gabriel, D., and Morand, S. (2010). Dopaminergic modulation of rapid reality adaptation in thinking. *Neuroscience* 167, 583–587. doi:10.1016/j.neuroscience.2010.02.044

Schnider, A., Mohr, C., Morand, S., and Michel, C. M. (2007). Early cortical response to behaviorally relevant absence of anticipated outcomes: a human event-related potential study. *Neuroimage* 35, 1348–1355. doi:10.1016/j.neuroimage.2007.01.047

Schnider, A., Nahum, L., Pignat, J., Leemann, B., Lövblad, K., Wissmeyer, M., et al. (2013). Isolated prospective confabulation in Wernicke-Korsakoff syndrome: a case for reality filtering. *Neurocase* 19, 90–104. doi:10.1080/13554794.2011.654221

Schnider, A., and Ptak, R. (1999). Spontaneous confabulators fail to suppress currently irrelevant memory traces. *Nat. Neurosci.* 2, 677–681. doi:10.1038/10236

Schnider, A., Ptak, R., Von Däniken, C., and Remonda, L. (2000a). Recovery from spontaneous confabulations parallels recovery of temporal confusion in memory. *Neurology* 55, 74–83. doi:10.1212/WNL.55.1.74

Schnider, A., Treyer, V., and Buck, A. (2000b). Selection of currently relevant memories by the human posterior medial orbitofrontal cortex. *J. Neurosci.* 20, 5880–5884.

Schnider, A., Valenza, N., Morand, S., and Michel, C. M. (2002). Early cortical distinction between memories that pertain to ongoing reality and memories that don't. *Cereb. Cortex* 12, 54–61. doi:10.1093/cercor/12.1.54

Schnider, A., Von Däniken, C., and Gutbrod, K. (1996a). The mechanisms of spontaneous and provoked confabulations. *Brain* 119, 1365–1375. doi:10.1093/brain/119.4.1365

Schnider, A., Von Däniken, C., and Gutbrod, K. (1996b). Disorientation in amnesia. A confusion of memory traces. *Brain* 119, 1627–1632. doi:10.1093/brain/119.5.1627

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* 30, 259–288. doi:10.1146/annurev.neuro.28.061604.135722

Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science* 275, 1593–1599. doi:10.1126/science.275.5306.1593

Schultz, W., and Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500. doi:10.1146/annurev.neuro.23.1.473

Schwaerzel, M., Heisenberg, M., and Zars, T. (2002). Extinction antagonizes olfactory memory at the subcellular level. *Neuron* 35, 951–960. doi:10.1016/S0896-6273(02)00832-2

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatr.* 20, 11–21. doi:10.1136/jnnp.20.1.11

Squire, L. R., Stark, C. E., and Clark, R. E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306. doi:10.1146/annurev.neuro.27.070203.144130

Squire, L. R., and Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annu. Rev. Neurosci.* 34, 259–288. doi:10.1146/annurev-neuro-061010-113720

Talland, G. A. (1961). Confabulation in the Wernicke-Korsakoff syndrome. *J. Nerv. Ment. Dis.* 132, 361–381. doi:10.1097/00005053-196105000-00001

Thorpe, S. J., Rolls, E. T., and Maddison, S. (1983). The orbitofrontal cortex: neuronal activity in the behaving monkey. *Exp. Brain Res.* 49, 93–115. doi:10.1007/BF00235545

Treyer, V., Buck, A., and Schnider, A. (2003). Subcortical loop activation during selection of currently relevant memories. *J. Cogn. Neurosci.* 15, 610–618. doi:10.1162/089892903321662985

Treyer, V., Buck, A., and Schnider, A. (2006). Selection of currently relevant words: an auditory verbal memory study using positron emission tomography. *Neuroreport* 17, 323–327. doi:10.1097/01.wnr.0000199457.78670.44

Van der Horst, L. (1932). Über die Psychologie des Korsakowsyndroms. *Monatsschr. Psychiatr. Neurol.* 83, 65–84. doi:10.1159/000164016

Wahlen, A., Nahum, L., Gabriel, D., and Schnider, A. (2011). Fake or fantasy: rapid dissociation between strategic content monitoring and reality filtering in human memory. *Cereb. Cortex* 21, 2589–2598. doi:10.1093/cercor/bhr049

Wallis, J. D. (2007). Orbitofrontal cortex and its contribution to decision-making. *Annu. Rev. Neurosci.* 30, 31–56. doi:10.1146/annurev.neuro.30.051606.094334

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Retrieval, monitoring, and control processes: a 7 Tesla fMRI approach to memory accuracy

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Memory research has been guided by two powerful metaphors: the storehouse (computer) and the correspondence metaphor. The latter emphasizes the dependability of retrieved mnemonic information and draws upon ideas about the state dependency and reconstructive character of episodic memory. We used a new movie to unveil the neural correlates connected with retrieval, monitoring, and control processes, and memory accuracy (MAC), according to the paradigm of Koriat and Goldsmith (1996a,b). During functional magnetic resonance imaging, subjects performed a memory task which required (after an initial learning phase) rating true and false statements [retrieval phase (RP)], making confidence judgments in the respective statement [monitoring phase (MP)], and deciding for either venturing (volunteering) the respective answer or withholding the response [control phase (CP)]. Imaging data pointed to common and unique neural correlates. Activations in brain regions related to RP and MAC were observed in the precuneus, middle temporal gyrus, and left hippocampus. MP was associated with activation in the left anterior and posterior cingulate cortex along with bilateral medial temporal regions. If an answer was volunteered (as opposed to being withheld) during the CP, temporal, and frontal as well as middle and posterior cingulate areas and the precuneus revealed activations. Increased bilateral hippocampal activity was found during withholding compared to volunteering answers. The left caudate activation detected during withholding compared to venturing an answer supports the involvement of the left caudate in inhibiting unwanted responses. Contrary to expectations, we did not evidence prefrontal activations during withholding (as opposed to volunteering) answers. This may reflect our design specifications, but alternative interpretations are put forth.

Keywords: memory confidence, memory retrieval, monitoring, movie, real-life events

INTRODUCTION

When considering the contribution of subject-controlled processes to memory performance, it is important to distinguish between two different properties of memory: quantity and accuracy (Klatzky and Erdelyi, 1985). Koriat and Goldsmith (1994, 1996a) and Herrmann et al. (1996) have shown that these two features have received rather different emphasis in current research practices. With the quantity-oriented and accuracy-oriented approaches to memory, two fundamentally different ways of thinking about memory have been introduced. These ways map onto the distinction between two memory metaphors, the storehouse (where memory is seen as a storehouse garnering items for a later retrieval and is therefore defined in terms of the number of items that can be recovered; Gruneberg and Morris, 1978; Roediger, 1980; Markowitsch, 1994, 2008) and the correspondence metaphor (that construes memory in terms of its capability to faithfully represent past events, rather than just in terms of the quantity of items that are remembered and therefore are remaining in store) (Koriat and Goldsmith, 1996b).

According to Koriat and Goldsmith (1996b), experimental, laboratory memory research is preponderantly quantity-oriented, while in everyday-life the importance of the accuracy-oriented framework is underscored. A common example that illustrates the difference between the two approaches pertains to eyewitness reports: according to the quantity-oriented approach it would be important how much information about an offender can be retrieved, while the accuracy-oriented framework concerns the question whether essential information (e.g., the facial features of an offender) can be remembered. Moreover accuracy measures assess executive components of memory control by evaluating the correctness of retrieved information, and whether certain information would be reported if someone had for example to act as a witness in court (Kelley and Sahakyan, 2003).

The paradigm of Koriat and Goldsmith enables a separated evaluation of quantity and accuracy. Memory quantity performance is defined as the input-bound percentage of statements that were correctly answered (e.g., conditional on the number of input items), whereas memory accuracy (MAC) performance is formalized as the output-bound percentage of statements that were correct (e.g., conditional on the number of output items). The output-bound accuracy measures uniquely reflect the dependability of the reported information, that is, the extent to which each reported item can be counted on to be correct (Goldsmith et al., 2002). MAC performance is tied to the individual competence of controlling the correctness of given answers and deciding to volunteer correct answers and withhold incorrect answers, respectively (see **Figure 1**).

The paradigm of Koriat and Goldsmith entails three different phases of recall in which different monitoring processes proceed. In the retrieval phase (RP) subjects are presented with a set of memory questions and are requested to answer each of them, even if they have to guess. However, this phase is executed under forced recall conditions and quantity as well as accuracy performance is equalized in the RP.

In the monitoring phase (MP) the monitoring process is activated, hence subjects are required to rate their confidence of whether the retrieved item is correct or not (0–100%). In the control phase (CP) subjects are free to decide whether to bet on the correctness of their answer or not (volunteering or withholding). The control mechanism operates by establishing a confidence threshold (response criterion) on the monitoring output: if the assessed probability of being correct passes the threshold, the answer is volunteered; otherwise the answer is withheld. The setting of the threshold is sensitive to the gain for giving a correct answer relative to the cost of delivering an incorrect response.

The impact of monitoring and control on (free-report) memory performance has been proven to depend on several elements, such as the monitoring effectiveness, the control sensitivity, and the response criterion setting (Koriat and Goldsmith, 1996b). The extent to which the assessed probabilities successfully discern correct from wrong candidate answers and weighing the relative payoffs for accuracy and quantity for coming up with an optimal criterion level are captured by the construct of monitoring effectiveness.

The control sensitivity is the degree to which volunteering or withholding of answers is in fact susceptible to the monitoring output response. The (report) criterion setting reveals the probability level that is appointed (set) in consonance with the incentive to be accurate (and contending demands for quantity and accuracy). The criterion setting or report control policy can be gaged as "the cut-off on each participant's assessed-probability-correct ratings that best predicts his or her actual volunteering-withholding decisions in the free-report phase" (Halamish et al., 2012, p. 2). These three factors strongly influence quantity and accuracy of memory performance and therefore their investigation is warranted when examining MAC (Goldsmith et al., 2002).

The aim of the current study is to implement the model of the strategic regulation of MAC and memory quantity performance by Koriat and Goldsmith into a functional magnetic resonance imaging (fMRI) design, in order to disentangle the neural correlates connected with the three main processes: retrieval, monitoring, and control and, additionally unravel the brain areas related to MAC performance. For the purpose of approximating real-life conditions, we used in the present study a short film with emotional material. During the scanning procedure, subjects had to respond to veridical and incorrect statements pertaining to the content of the movie. This format shares a similitude to the study

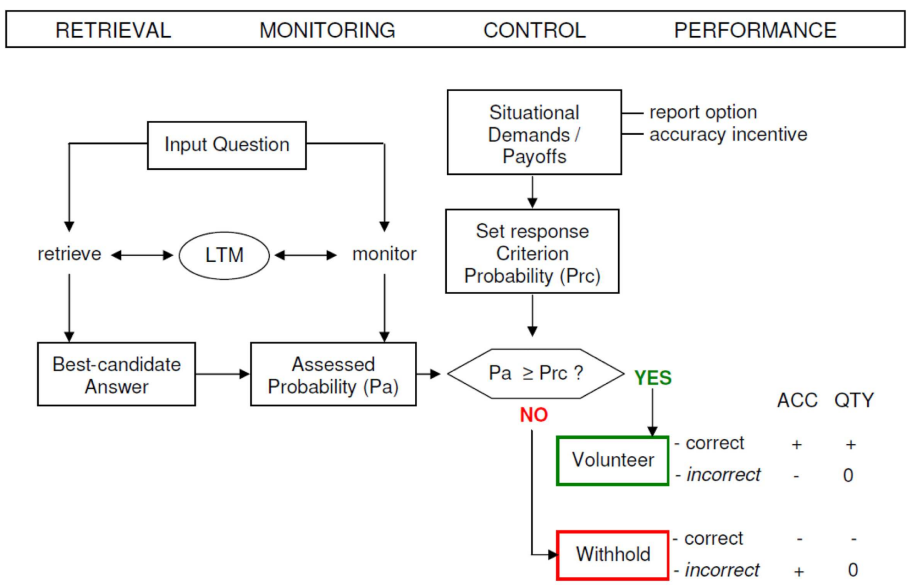


FIGURE 1 | A schematic model of the strategic regulation of memory accuracy and memory quantity performance. Performance effects are signified by plus (+ = increase), minus (− = decrease), and zero (0 = no effect). LTM, long-term memory; ACC, accuracy; QTY, quantity; Pa, assessed probability; Prc, response criterion probability (modified from Koriat and Goldsmith, 1996b).

of Mendelsohn et al. (2010): during the videotape audiovisual material was presented, while the fMRI-scanning phase contained only written statements. These statements had not been presented previously and therefore it is assumed that they "could not be answered properly without mentally reconstructing studied material" (Mendelsohn et al., 2010, p. 1). By employing this design we had the goal to come close to eyewitness testimony circumstances, where the testifiers might have watched a criminal event and subsequently, when they appear in court, they have to respond verbally.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-nine subjects [14 male (mean age = 26, SD = 2.8, min = 22, max = 31 years), 15 female (mean age = 24.13, SD = 3.4, min = 20, max = 30 years)] without prior history of psychiatric conditions (including gambling problems) or neurological diseases (as determined by thorough screening) and with normal or corrected to normal vision participated in the experiment. The study was approved by the local ethics committee. Female and male subjects did not significantly differ with respect to their mean age (female versus male, $T = 0.55$, $p = 0.592$). All participants (mean age = 25, SD = 3.2, min = 20, max = 31 years) were right-handed, as assessed by the Edinburgh inventory (Oldfield, 1971), and native speakers of German. Participants were recruited from the University of Bielefeld community. Written consent for taking part in the study and publication of study's data in an anonymized form was obtained from all the participants. The participants received course credits or 20 Euros (plus the bonus they gained for correctly volunteering during the scanning procedure).

Neuropsychological tests

Participants underwent neuropsychological testing including standard assessments of intelligence, working memory, long-term explicit memory, visuo-constructive abilities, executive functioning, and attention. Intelligence was evaluated with the LPS (Leistungsprüfsystem)-4 (Horn, 1983), handedness, with the Edinburgh Handedness Inventory (Oldfield, 1971) and attention and concentration, with the d2-Test (Brickenkamp and Zillmer, 1998), the Trail Making Test A (Lezak, 1995), and the forward digit span subtest of the Wechsler-Memory Scale-Revised (Härting et al., 2000). Anterograde explicit memory was tested with the Verbal Learning and Memory Test (Helmstaedter et al., 2001) and the Rey–Osterrieth Complex Figure (Lezak, 1995) and working memory was evaluated with the backward digit span subtest of the Wechsler-Memory Scale-Revised (Härting et al., 2000). Executive functions and decision-making were examined with the Game of Dice task (Brand et al., 2005; Brand and Markowitsch, 2010) and the Trail Making Test B (Lezak, 1995). Trail Making Test B served also for testing cognitive flexibility. Verbal fluency tasks (animal words and words starting with the letters F, A, and S) (Lezak, 1995) were given to test word fluency as well as executive functions. In order to aid the exclusion of subjects with personality or psychiatric problems, three scales were given to the participants for self administration, such as the Beck Depression Inventory (BDI; Beck et al., 1995), the Freiburg Personality Inventory (FPI; Fahrenberg et al., 2001), and the Brief Symptom Inventory (BSI; Derogatis, 1993).

STIMULI

Videotape

A short film named "The New Cat," with an approximate duration of 6 min and emotional material appropriate for students was shown on a computer screen that was 13″ in size. For a consistent and sufficing volume external boxes were used. The film was shown about 2 h prior to the scanning phase. This film by Ziv Shachar (originally entitled "GATO-NOVO") was identified as being an adequate stimulus material for the research project "The assessment of eyewitness memory: a multi componential, correspondence oriented approach" by research colleagues from Haifa University (Koriat et al., 2000), who obtained the rights to utilize it for research purposes and who used it for behavioral, but not for neuroimaging experiments within the common project financed by the European Commission (De Mulder et al., 2010). (The design resembles that of Pansky and Tenenboim, 2011, though in that study a 6.5 min slide show had been used instead of a film). The soundtrack of the film (originally in Hebrew) was translated to German and English, respectively, to allow its use by the German and English research EU partners. The film has a good range of scenic details, well suited for the fMRI procedure. The movie is about a young adult man who is fond of dogs, but has problems with keeping them in the house, because they make dirt. He decides to have a cat as a pet, but he gets shortly in trouble with this, because he treats the cat like he would treat a dog. After only 1 day, the cat jumps from the window sill and is run over by a car driven by a young woman. Later the young woman and the main character fall in love with each other and they bury together the cat. The pair then moves to live together; the woman gives a dog as a present to the young man. None of the participants in the study indicated having seen the video before. Furthermore subjects were not communicated that their memory of the movie would be probed later ("incidental" encoding condition).

Statements

About 180 statements concerning the story of the film were constructed, of which one half concerned true details and the other half contained incorrect details of the film. Moreover, all true and all false statements were consistently related to different categories, like content, perception, and action. The formulated statements were short (with a range between 5 and 10 words in the German language version), in order to improve their readability on the screen inside the scanner. We attempted to have approximately similar numbers of items for the different categories and also to match the statements with respect to difficulty or complexity (see Appendix).

Experimental tasks

The tasks used during event-related fMRI procedure required the subjects to evaluate correct and incorrect statements from the videotape they saw before. In sum 180 statements appeared on a computer screen in a random order. Each statement had to be assessed with respect to its quality as being true or false (RP). This was followed by a confidence rating offering the options of three increments, namely 100% confidence, 75% confidence, and 50% confidence (MP). For further analyses we decided to differentiate between high (100%) and low confidence (combining 50

and 75%). In the next step, subjects had to decide whether to volunteer (bet) or withhold the answer (CP). Volunteering consisted of expressing the will to bet on the correctness of the given answer. An explicit bonus system of moderate incentive was implemented to motivate accurate responding. All participants were recompensed according to the number of bonus points. If a correct answer was volunteered one bonus point could be earned; if an incorrect answer was volunteered, one bonus point could be lost. When deciding for withholding the response, no bonus points were granted or deducted, irrespective of the correctness of the answer. For the baseline a fixation cross was presented to complete the foregone sequence and draw attention to the next sequence (see **Figure 2**).

During the fMRI measurement, subjects made their choices using three fingers of their right hand (index finger, middle finger, and ring finger) on a three button response device. Random jitter was included to prevent correlation of event regressors. For this, statements were presented between 3 and 5 s, and the confidence retrieval, the question for volunteering/withholding as well as the fixation cross were illustrated between 2 and 3 s. The whole run took about 43 min. In order to prevent head movements throughout the scan, the experiment was divided into two consecutive scans, each containing one half of the statements. Each run lasted an average of 17 min. For stimulus presentation and response collection, the software Presentation 9.0[1] (Neurobehavioral Systems, Albany, CA, USA) was used. During the fMRI experiment, the stimulus display was back-projected onto a screen mounted on a custom head coil.

Pre-scanning procedure

In order to get familiarized with the experimental set-up, subjects took part in a presentation of neutral statements adapted for utilization inside the scanner. Some of these 45 statements were

[1]http://www.neurobs.com

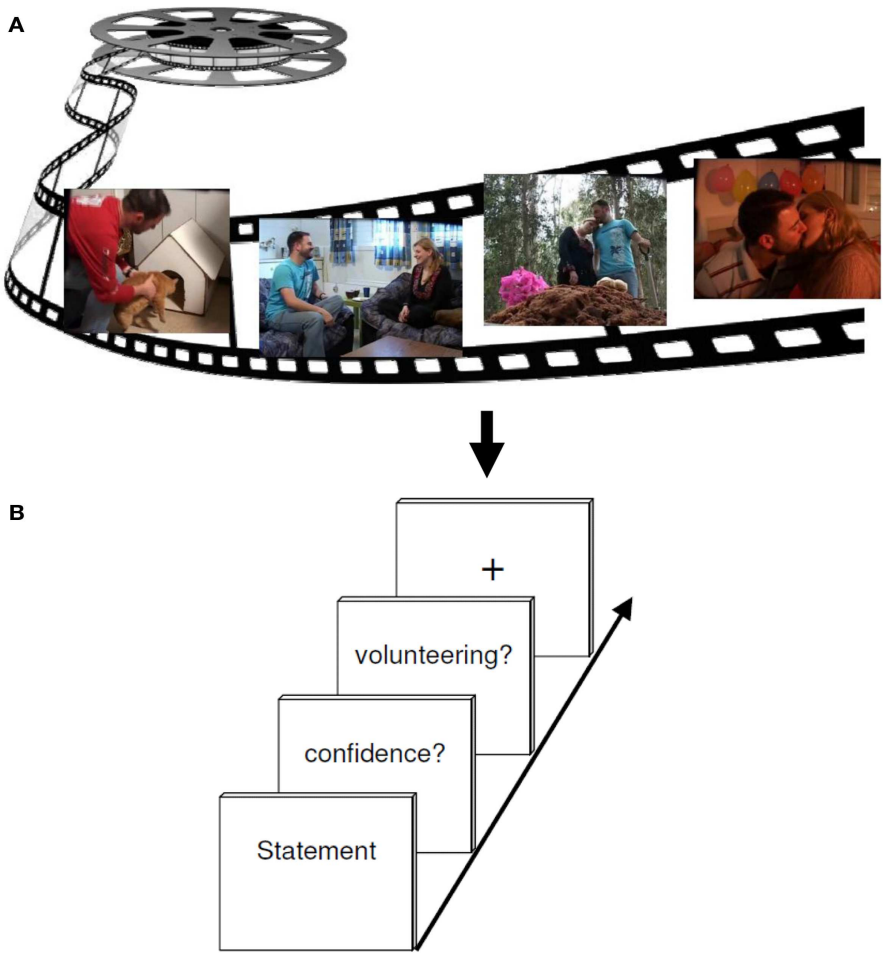


FIGURE 2 | Experimental design. (A) The encoding session consisted of watching a 6 min emotional film in a quiet room. **(B)** About 2 h later, participants performed a test session while undergoing an fMRI brain scan. Each retrieval task trial included either a correct or incorrect statement regarding events in the movie, to which subjects had to responded either "yes" (true) or "no" (false) (RETRIEVAL phase). Subsequently, participants had to rate their confidence (MONITORING phase) about the foregoing response (high versus low secureness) and had to decide either to volunteer or to withhold their answer (CONTROL phase).

true and some of them were false, e.g., "elephants have thick skin." Subjects completed the pre-testing-learning phase on the same PC the videotape was shown earlier and used the numbers "1" "2" and "3" of the PC keyboard. It was important that subjects deliberated on the statements, in order to get used to the available time slot. The instruction was similar to the fMRI-scanning procedure. The goal of the pre-scanning procedure was to make sure that subjects internalize the instruction and automated button-pushing, in order to secure an accurate scanning procedure. All participants reached the required cut-off value, which was saved in a txt file and therefore made available for an evaluation. For stimulus presentation and response collection, the software Presentation 9.0 (Neurobehavioral Systems, Albany, CA, USA; see text footnote 1) was utilized.

MR technical parameters

Functional MR images were acquired on a Siemens Magnetom Investigational Device 7T syngo MR B15 with echo planar imaging (EPI) capability. Head motion was restricted using expandable foam pads that surrounded the head. Stimuli were presented on a screen. Multislice T2*-weighted echo planar images were achieved from a gradient-echo sequence with the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 29 ms, field of view (FOV) = 230 mm, flip angle = 76°, slice thickness = 4 mm. About 30 axial slices were oriented in the plane of the anterior-posterior commissure and covered the whole brain. For each subject, additional high-resolution anatomical images were acquired using the 3D T1-weighted magnetization prepared, rapid acquisition gradient echo (MP-RAGE) sequence with the parameters: TR = 2300 ms, TE = 3.93 ms, inversion time (TI) = 1100 ms, flip angle = 12°, FOV = 256 × 256 mm, matrix size = 1.0 mm × 1.0 mm × 1.0 mm, 160 sagittal slices with a thickness of 1 mm (Poser and Norris, 2009; Poser et al., 2010).

Image processing and data analysis

Functional volumes were analyzed with SPM5[2] (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 7 (The Mathworks Inc., Natick, MA, USA). The images were realigned, normalized into the Montreal Neurological Institute (MNI) coordinate space and smoothed with a 5 mm × 5 mm × 5 mm Gaussian kernel (full width half maximum).

Parameter estimates of the resulting general linear model were calculated for each subject and each voxel. For population inference, a second level analysis was performed, using the contrast estimates for the simple effect of each experimental condition.

Differential contrasts of interest were calculated according to the experimental factors RP (correct answer versus incorrect answer, and vice versa), MP (high confidence versus low confidence, and vice versa), and CP (volunteering versus withholding, and vice versa) as well as RP versus MP (and vice versa), RP versus CP (and vice versa), and MP versus CP (and vice versa) to assess differential modulation of the BOLD signal induced by each factor. To detect only MAC (without an overlap to quality) according to the model of Koriat and Goldsmith (see **Figure 1**) the factor MAC was calculated: MAC+ (withholding an incorrect answer leads to an increase in MAC) versus MAC− (volunteering an incorrect answer leads to a decrease in MAC) (and vice versa).

The statistical threshold for within- and between-group comparisons was set to $p < 0.001$, corrected for multiple comparisons at the cluster level. This threshold was required due to the combination of a high Tesla Scanner and a rather complex experimental design.

Localization of activations

SPM_T maps resulting from the group analysis were superimposed onto a group mean MR image which was calculated from the normalized anatomical T1-images of each subject (see above). Standard stereotactic coordinates of voxels showing local maximum activation were determined within areas of significant relative changes in neural activity associated with different experimental conditions. Maxima were anatomically localized and labeled with an anatomical SPM5 toolbox, namely AAL, which refers to the Automated Anatomical Labeling map which is a three-dimensional map containing 116 brain regions co-registered to standard MNI space. MNI coordinates refers to a standard brain imaging coordinate system developed by the MNI (Tzourio-Mazoyer et al., 2002).

RESULTS

BEHAVIORAL DATA

Neuropsychological testing

Individual neuropsychological data were within the range of reference population norms for all tests which were administered.

Responding behavior during scanning

For the differential contrasts defined in the fMRI experiment T-tests for paired samples were executed to analyze subjects' response behavior. T-tests revealed that subjects responded to the statements mainly correctly (RP: correct answer versus incorrect answer, $T = 23.59$, $p < 0.001$). During retrieval process, different responding pattern can be distinguished: (A) to assume a true statement (hit), (B) to decline a true statement (miss), (C) to decline a false statement (correct rejection), and (D) to assume a false statement (false alarm). Correct responding is therefore defined as either correct rejection or hit, in contrast to incorrect responding that represents either false alarm or miss. The results of the present study show that when a statement was answered correctly this was a consequence of correct rejection significantly more often than it was resulting from a hit (correct rejection versus hit, $T = 6.56$, $p < 0.001$). When a statement was answered incorrectly this was because of a miss significantly more often than it was due to a false alarm (miss versus false alarm, $T = 8.57$, $p < 0.001$).

No significant difference can be reported for the confidence rating of the statements (MP: high confidence versus low confidence, $T = -1.43$, $p = 0.16$). Moreover, the analyses reveal that subjects rather volunteered an answer instead of withholding it (CP: volunteering versus withholding, $T = 2.1$, $p < 0.05$). Participants show respectively a significant increase in MAC (MAC+ versus MAC−, $T = 9.18$, $p < 0.001$). Data are displayed in **Figure 3**.

[2]http://www.fil.ion.ucl.ac.uk/spm

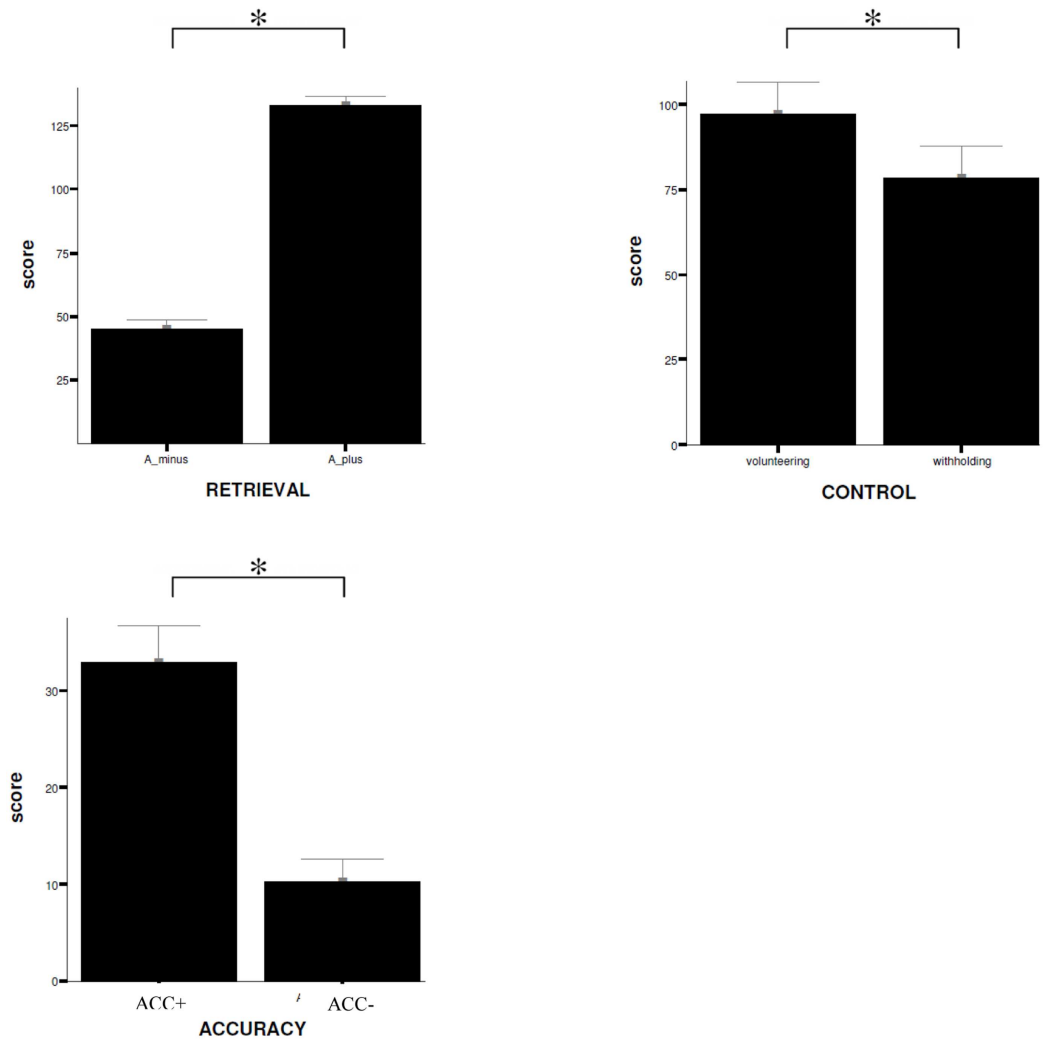


FIGURE 3 | Behavioral data. Comparison of mean ratings (±SD) given by the subjects on items during scanning procedure for the different experimental conditions, RETRIEVAL, CONTROL, and ACCURACY. W+, volunteering; W−, withholding; SD, standard deviation; *trend of statistical significance ($p < 0.05$, uncorrected). A_ minus = incorrect answering; A_ plus = correct answering.

fMRI DATA

Retrieval process (correct versus incorrect responding)

The main effect of the correct relative to incorrect (A+ > A−) answers revealed significant differential bilateral activations of the precuneus and activations of the left hippocampus, the left insula, left middle temporal gyrus (MTG), and right lingual gyrus ($p < 0.001$, uncorrected). The reverse contrast (A− > A+) did not show any differential activation. Data are displayed in **Table 1** and **Figure 4**.

Monitoring process (high confidence versus low confidence)

Areas of significant differential activation revealed by high confidence relative to low confidence (S+ > S−) ratings were located bilaterally in the fusiform gyrus and the left lingual gyrus and the left parahippocampal gyrus ($p < 0.001$, uncorrected) (**Table 2A**; **Figure 5A**). The reverse contrast (S− > S+) demonstrated, amongst others, bilateral activation of the hippocampus, the angular gyrus, precentral gyrus, lingual, middle occipital, inferior parietal and postcentral gyri, putamen, Rolandic operculum, different temporal and frontal and occipital regions, the left precuneus, and the right insula ($p < 0.05$, False Discovery Rate-FDR corrected); at $p < 0.05$, Family Wise Error (FWE) corrected the left precuneus was activated. See **Table 2B** and **Figure 5B** for detailed information.

Control process (volunteering versus withholding)

Volunteering relative to withholding (W+ > W−) produced bilateral activations of temporal, frontal, and cingulate regions, namely of the MTG, the superior temporal pole, the left middle frontal and left inferior frontal cortex (pars opercularis), the left precuneus and the right posterior cingulate cortex ($p < 0.001$, uncorrected) (see **Table 3A**; **Figure 6A**). The reverse contrast, namely, withholding (W− > W+), revealed bilateral activation of the hippocampus, the left caudate nucleus, the left Heschl region, and the left postcentral

Table 1 | Group activations for the contrast between correct versus incorrect answers (RP), $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates**		
		x	*y*	*z*
CORRECT > INCORRECT				
Precuneus	L	−14	−48	40
	R	14	−16	36
Hippocampus	L	−20	−36	0
Insula	L	−36	−32	22
Lingual gyrus	R	10	−40	2
Middle temporal gyrus	L	−42	−50	8

Brain regions within the boundaries of the AAL atlas.*

**AAL refers to the Automated Anatomical Labeling map which is a three-dimensional map containing 116 brain regions co-registered to standard MNI space.*

***MNI coordinates refers to a standard brain imaging coordinate system developed by the Montreal Neurological Institute.*

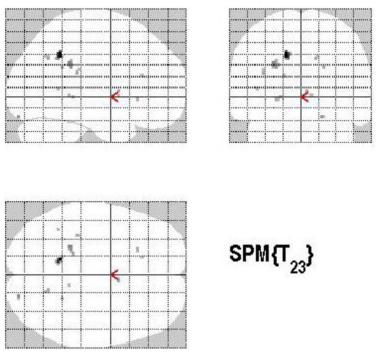


FIGURE 4 | Group activations for the contrast between correct versus incorrect answers (RETRIEVAL). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 1** for the exact MNI coordinates.

gyrus ($p < 0.001$, uncorrected). Data are presented in **Table 3B** and **Figure 6B**.

Monitoring versus retrieval process

The main effect of monitoring relative to retrieval revealed significant differential bilateral activations of the inferior occipital gyrus, precuneus, MTG, left middle cingulate cortex, left anterior and posterior cingulate cortex, left middle and superior frontal gyri ($p < 0.001$, uncorrected) (**Table 4**; **Figure 7**). The reverse contrast, retrieval (relative to monitoring), did not reach statistical significant activation.

Control versus retrieval

Areas of significant differential activation revealed by control relative to retrieval were located in the left middle frontal gyrus, left MTG, right fusiform gyrus, right putamen, right Rolandic operculum, and the right superior temporal gyrus (STG) ($p < 0.001$, uncorrected) (See **Table 5**; **Figure 8**). Again, the reverse contrast, retrieval (relative to control) did not show any differential activation.

Monitoring versus control process

The main effect of monitoring relative to control consisted of significant activations of the right STG ($p < 0.001$, uncorrected) (See **Table 6**; **Figure 9**). Due to the fact that only one region reached statistical significance this contrast will not be discussed here. The reverse contrast, control (relative to monitoring), did not reveal any significant activation.

Memory accuracy (MAC+ versus MAC−)

There are different ways of defining MAC; in the present study the manner of conceptualizing MAC was influenced by the paradigm put forth by Koriat and Goldsmith (1996a,b). MAC was defined as withholding an *incorrect* answer, whereas memory inaccuracy was related to volunteering an *incorrect answer* (See **Figure 10**). The main effect of high MAC relative to low MAC revealed significant differential bilateral activations of the STG, the supramarginal gyrus, left hippocampus, left Heschl region, the right superior temporal pole, MTG, and the right precuneus ($p < 0.001$, uncorrected), depicted in **Table 7A** and **Figure 11A**. The reverse contrast, low accuracy (relative to high accuracy), revealed activation only of the left hemisphere, namely the insula and the superior frontal gyrus ($p < 0.001$, uncorrected), illustrated in **Table 7B** and **Figure 11B**.

DISCUSSION

The current study had the goal of unveiling the neural mechanisms connected with retrieval, monitoring, and control processes according to the memory paradigm of Koriat and Goldsmith (1996b) and, furthermore of identifying the neural underpinnings of MAC. Below we discuss the responses of selected regions that were predicted on grounds of previous findings.

RETRIEVAL PROCESS (CORRECT VERSUS INCORRECT RESPONDING)

The factor RP (retrieval; correct versus incorrect responding) induced a significant effect in the behavioral rating during the scanning procedure: subjects gave more correct than incorrect answers, however, this was in general a consequence of correct rejection (instead of a hit). One could argue that these behavioral results resemble a distinctiveness heuristic (Schacter et al., 1999; Gallo et al., 2008; Koriat et al., 2008; McDonough and Gallo, 2012). Gallo (2011) noted that, when participants expect distinctive memories, they seem to be biased to avoid false alarms rather than enhancing true memory decisions (hits). When incorrect answers were given in our study, this resulted basically from a miss (instead of a false alarm). This finding indicates that subjects were able to correctly discriminate between correct and incorrect answers and moreover responded rather cautiously, avoiding risky decisions. Incidentally, no participant showed a tendency for risk-taking behavior on the Game of Dice task (Brand et al., 2005; Brand and Markowitsch, 2010).

When responding correctly instead of giving false (incorrect) answers brain activation was found mainly in areas that are agreed upon to be involved in mnemonic processing. In consonance

Table 2 | Group activations for the contrast between high versus low confidence (MP), $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
(A) HIGH CONFIDENCE > LOW CONFIDENCE				
Fusiform gyrus	R	34	−48	−4
	L	−34	−50	−10
Parahippocampal area	L	−28	−42	−6
Lingual gyrus	L	−32	−48	−2
(B) LOW CONFIDENCE > HIGH CONFIDENCE				
Precuneus	L	−8	−50	36
	L	−2	−56	30
	L	−2	−64	24
Cuneus	L	−2	−80	28
	R	12	−96	10
Middle temporal gyrus	L	−44	−52	4
	L	−52	−62	4
	L	−52	−42	10
	R	56	−62	2
	R	54	−68	14
	R	62	−54	12
	R	52	−52	10
	R	60	−50	0
	R	58	−36	−8
Superior temporal pole	L	−44	22	−18
	L	−54	12	−8
Superior temporal gyrus	R	62	−50	20
	L	−60	−30	22
	L	−52	−34	10
	R	38	−32	12
	R	56	−44	20
Inferior temporal gyrus	R	58	−60	−6
Fusiform gyrus	L	−32	−24	−26
Insula	R	40	0	0
	R	44	18	0
	R	36	−12	22
	R	36	−18	4
Middle occipital gyrus	R	52	−68	26
	R	30	−72	22
	R	38	−72	16
	R	36	−84	30
	L	−24	−86	10
	L	−32	−88	14
Superior occipital gyrus	L	−14	−84	22
Inferior occipital gyrus	R	30	−86	−16
Parahippocampal area	L	−22	−26	−20
Hippocampus	R	24	−20	−16
	L	−30	−6	−26
Putamen	L	−22	12	0
	L	−30	2	−2
	R	22	14	−2
Inferior frontal gyrus pars opercularis	L	−52	12	6
	L	−34	24	−12
	L	−52	14	20
	L	−58	12	16
Inferior frontal gyrus pars triangularis	L	−44	40	0
	L	−46	32	16
Superior frontal gyrus medial	L	2	36	38
Superior frontal gyrus	L	−24	54	6
Middle frontal gyrus	L	−38	24	40
Supramarginal gyrus	L	−48	−44	34
	L	−56	−52	34
	L	−52	−30	24
Postcentral gyrus	R	−40	−32	10
Lingual gyrus	L	−14	−56	−10
	L	−16	−68	−6
	R	14	−60	−8
Precentral gyrus	R	54	−4	40
	L	−42	−2	30
Postcentral gyrus	L	−46	−12	38
	R	58	−22	42
	R	54	−16	40
Posterior cingulate cortex	L	−6	−44	8
Middle cingulate cortex	R	6	−16	34
	R	10	−30	32
Calcarine sulcus	L	−12	−80	12
	L	−14	−66	4
	L	−14	−72	8
Inferior parietal gyrus	L	−54	−48	50
	L	−46	−58	46
	L	−42	−56	48
	R	32	−42	52
	R	58	−48	40
Rolandic operculum	R	50	−18	12
	R	52	−10	18
	R	46	−12	20
	L	−60	−6	12
Angular gyrus	R	56	−48	30
	R	50	−66	40
	L	−46	−58	34
Paracentral lobule	R	16	−42	50

Brain regions within the boundaries of the AAL atlas.*

with other previous studies, we evidenced activation of the left hippocampus during correct responding (in contrast to incorrect answering). In particular, our finding supports the results of a relatively recent study of Mendelsohn et al. (2010) analyzing differential BOLD responses as a function of correctness in the left hippocampus. In this study, young adults saw a documentary movie. A week later they had to accept or reject factual or fictitious verbal statements about the movie while undergoing functional MRI.

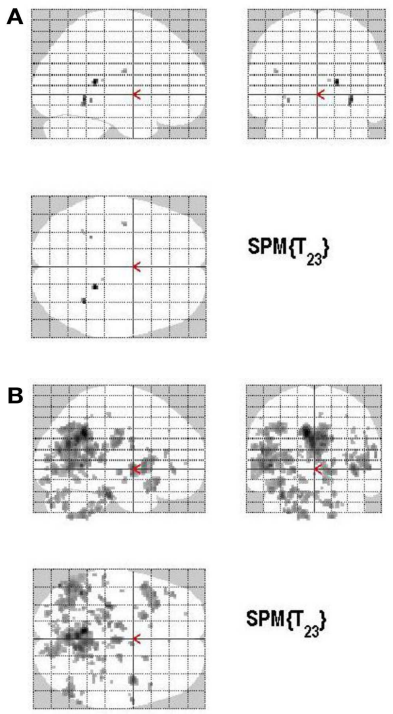


FIGURE 5 | (A) Group activations for the contrast between high versus low secureness (MONITORING). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 2A** for the exact MNI coordinates. **(B)** Group activations for the contrast between low versus high secureness (MONITORING). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 2B** for the exact MNI coordinates.

Table 3 | (A,B) Group activations for the contrast between volunteering versus withholding (CP), $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
(A) VOLUNTEERING > WITHHOLDING				
Superior temporal pole	R	44	20	−24
	L	−48	10	−22
Middle temporal gyrus	R	50	0	−26
	L	−52	−46	12
Posterior cingulate cortex	R	6	−38	10
Middle cingulate cortex	R	12	−40	48
Middle frontal gyrus	L	−22	48	26
Inferior frontal gyrus pars opercularis	L	−36	12	14
Precuneus	L	−10	−44	46
(B) WITHHOLDING > VOLUNTEERING				
Heschl region	L	−44	−14	6
Hippocampus	L	−28	−18	−16
	R	28	−16	−22
Caudate nucleus	L	−14	−8	18
Postcentral gyrus	L	−54	−10	24

Brain regions within the boundaries of the AAL atlas.*

The laterality of hippocampus activations during recall and the degree to which hippocampus subserves recollection versus recognition are however topics of ongoing debate (Gilboa et al., 2004, 2006; Addis et al., 2012). Some authors concluded that hippocampus selectively supports recollection, whereas others proposed that hippocampus is equally implicated in familiarity and recollection (Wixted and Squire, 2011; Markowitsch and Staniloiu, 2012). Wixted and Squire (2011) put forth the idea that when Remember and Know judgments are equated for strength at high level, hippocampal activity is elevated to a similar degree for Remember and Know judgments. A recent study however provided findings consistent with the view that hippocampus offers selective support for recollection and fails to respond to adjustments in familiarity strength and does not sustain strength-matched familiarity, which is sustained by perirhinal cortex (Kafkas and Montaldi, 2012). And another new investigation sets the foundation for a compromise, by showing that both dual-process and strength theories are partly correct (Hayes et al., 2011). Ross et al. (2009) proposed that the hippocampus may play a role in disambiguation, which is in sequence organization during recollection. Rutishauser et al. (2008), using single unit recordings, observed that spike activity in hippocampus correlated positively with successful recall of previously perceived stimuli.

With respect to laterality, the left hippocampus was related to verbal memory tasks (Frisk and Milner, 1990). It was also found to facilitate general coherence of an episode or a scene and play a role in self projection of oneself in comparison to another. Additionally it was linked to context dependant recall of episodic information and vividness of details (Viard et al., 2012). The age of participants can also affect the laterality, with older people showing greater right hippocampus activation or bihemispheric activation during recall of episodic information than younger people (Oddo et al., 2010).

An interesting finding however comes from a recent review that showed that specific cues (verbal) associated to *strictly* episodic events elicited higher left (posterior) hippocampal activation than episodic events triggered by specific cues (Oddo et al., 2010; but see also Addis et al., 2012; Viard et al., 2012). This report lends support to the idea that the left hippocampal activation during correct answering in our study might have reflected a cued recollection experience. Similarly to Mendelsohn et al. (2010), we could argue that the statements presented during the fMRI-scanning acted as verbal cues for mentally recasting and recollecting the material presented in the film. On the other hand, several authors that looked at the hippocampus and processing of novel information (Tulving et al., 1994), found that the left hippocampus was activated during conditions that contained novel information (verbal or pictorial) (Poppenk et al., 2008; Hashimoto et al., 2012). These results are interesting in the light of our behavioral findings; as mentioned above, when participants answered a statement correctly, this was much more frequently the consequence of a correct rejection than of a hit. According to this line of

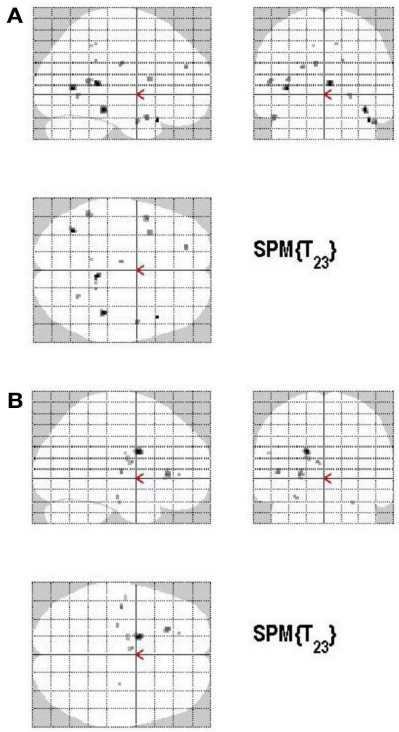


FIGURE 6 | (A) Group activations for the contrast between volunteering versus withholding (CONTROL). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 3A** for the exact MNI coordinates. **(B)** Group activations for the contrast between withholding versus volunteering (CONTROL). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 3B** for the exact MNI coordinates.

Table 4 | Group activations for the contrast between MP versus RP, $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
MP > RP				
Precuneus	R	6	−52	20
	R	12	−58	24
	L	−6	−54	8
Middle cingulate cortex	L	−12	−50	36
	L	0	−32	36
Posterior cingulate cortex	L	−6	−36	30
Anterior cingulate gyrus	L	0	40	10
	L	−2	38	12
Inferior occipital gyrus	L	−34	−86	−8
	R	36	−80	−4
Middle occipital gyrus	R	40	−76	2
Middle frontal gyrus	L	−34	44	16
Superior frontal gyrus medial	L	−2	56	22
Middle temporal gyrus	L	−48	−70	18
	L	−40	−54	12
	R	50	−72	2
	R	50	−50	4

Brain regions within the boundaries of the AAL atlas.*

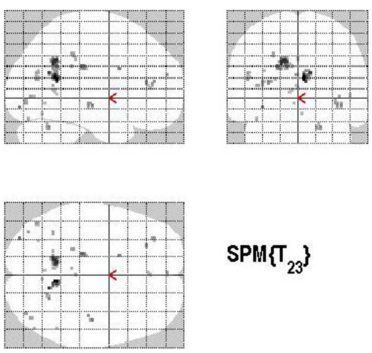


FIGURE 7 | Group activations for the contrast between MONITORING versus RETRIEVAL. Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 4** for the exact MNI coordinates.

thought, the left hippocampal activation during correct answers may alternatively (or additionally) reflect a correct rejection of novel, unstudied material (Düzel et al., 2003). One could speculate that the activation of the hippocampus may have indicated the detection/encoding of novel material (Düzel et al., 2003; Friedman et al., 2011). Alternatively, the observed activation might have signified a recollection rejection strategy, which is a plausible strategy in this population with intact working memory capacity (Koriat et al., 2008; Leding, 2012).

In our study, we also found activation in the lingual gyrus, an area that was described to be more active for correct than for incorrect (lag) judgments (Greve et al., 2010). The lingual gyrus was described as being part of the default-mode network and has been implicated in the generation of visual mental images, visual details of actual past events and "image content that is accessed via verbal materials" (Greve et al., 2010, p. 7103). Leshikar et al. (2012) reported task-selective memory effects for visual imagery (a monotonic increase in activity according to vividness) in the left precuneus as well as left occipital and right lingual gyri. In a functional imaging study by Gilboa et al. (2004) context-rich memories were associated with increased activity in right precuneus and bilateral lingual gyrus independently of remoteness. Addis et al. (2009) identified activations of lingual gyrus (and other posterior visual areas) during recall of actual past events as well as during construction (imagination) of past or future episodes; however, the activation was higher during the first condition in comparison to the last two conditions. The higher activation of the lingual gyrus during the recall (recollection) of actual past events was interpreted as being in line with the sensory reactivation or reinstatement hypothesis (Nyberg et al., 2000; Wheeler et al., 2000; Schacter and Loftus, 2013).

Table 5 | Group activations for the contrast between CP versus RP, $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
CP > RP				
Middle temporal gyrus	L	−42	−68	20
	L	−52	−46	8
Superior temporal gyrus	R	42	−34	12
Middle frontal gyrus	L	−32	44	16
Fusiform gyrus	R	34	−50	−4
Rolandic operculum	R	40	−32	18
Putamen	R	28	−16	4

Brain regions within the boundaries of the AAL atlas.*

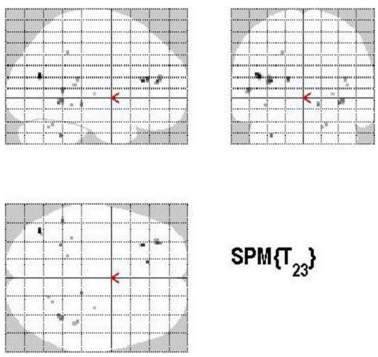


FIGURE 8 | Group activations for the contrast between CONTROL versus RETRIEVAL. Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 5** for the exact MNI coordinates.

Table 6 | Group activations for the contrast between MP versus CP, $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
MP > CP				
Superior temporal gyrus	R	46	−4	−14

Brain regions within the boundaries of the AAL atlas.*

Another interesting result yielded by our study concerns the bilateral activation of the precuneus in combination with the hippocampus. This result is related to the finding of hippocampal connectivity to the left precuneus in a recollection network (in contrast to familiarity) (Dörfel et al., 2009). Increased activity of precuneus was demonstrated for recollected items relative to misses, correct rejections, and strong familiarity (Kafkas and Montaldi, 2012). In a recent analysis, Kim (2013) showed that default-mode network areas, including the left precuneus,

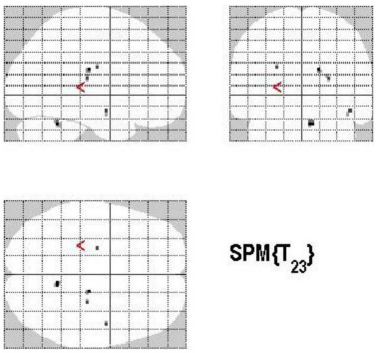


FIGURE 9 | Group activations for the contrast between MONITORING versus CONTROL. Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 6** for the exact MNI coordinates.

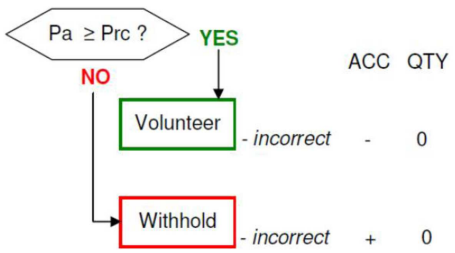


FIGURE 10 | Memory accuracy and inaccuracy according to the memory paradigm (cf. Figure 1 for abbreviations).

exhibited greater old/new (hit more than correct rejection) effects during a source-retrieval testing paradigm than during an item-retrieval task. This was interpreted as reflecting an enhanced ecphoric processing during the first testing paradigm (Kim, 2013). Addis et al. (2009) demonstrated via fMRI precuneus activations during both recollection of actual past events and construction of past or future events; however the construction-related tasks were accompanied by "greater percent signal change" in precuneus in comparison to the recollection-task. A PET study that investigated the neural correlates of true autobiographical memories and fictitious autobiographical memories found that fictitious autobiographical memories were associated with higher activations in the (left) precuneus than true autobiographical memories (Markowitsch et al., 2000). Cavanna and Trimble (2006) advanced the idea that there may be a functional dissociation within the precuneus; in particular, they proposed that the posterior precuneus may be associated with successful retrieval attempts, while the more anterior portion may be engaged in the retrieval mode via mental imaging. Memory-related imagery was in fact associated with significant activations of the anterior precuneus bilaterally in a seminal study, using positron emission tomography, conducted by Fletcher et al. (1995). In a recent fMRI study, Huijbers et al. (2011) however found the ventral precuneus to be associated with successful retrieval, but with unsuccessful imagery performance

Table 7 | (A,B) Group activations for the contrast between MAC+ versus MAC− (memory accuracy), $p < 0.001$, uncorrected.

Anatomical region	Side	MNI coordinates		
		x	*y*	*z*
(A) MAC+ > MAC−				
Superior temporal gyrus	L	−52	−28	12
	L	−60	−30	14
	R	62	−22	12
Superior temporal pole	R	52	4	−2
Middle temporal gyrus	R	48	−38	4
Hippocampus	L	−24	−40	0
Supramarginal gyrus	R	58	−38	32
	R	56	−36	34
	L	−62	−24	16
Heschl region	L	−32	−28	6
Precuneus	R	12	−42	46
(B) MAC− > MAC+				
Superior frontal gyrus medial	L	2	50	22
	L	0	46	32
	L	−8	60	8
Superior frontal gyrus	L	−14	60	8
Insula	L	−36	26	4

Brain regions within the boundaries of the AAL atlas.*

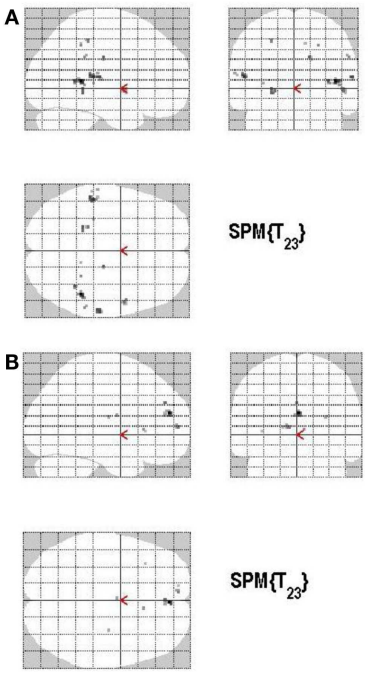


FIGURE 11 | (A) Group activations for the contrast between ACC+ versus ACC− (ACCURACY). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 7A** for the exact MNI coordinates. **(B)** Group activations for the contrast between ACC− versus ACC+ (ACCURACY). Activations are superimposed on the anatomical group mean image (see Materials and Methods), depicting statistically significant relative increases in neural activity at $p < 0.001$, uncorrected. See **Table 7B** for the exact MNI coordinates.

(including auditory imagery performance). The authors subsequently speculated that the activation of ventral precuneus during unsuccessful imagery may have reflected the processes of generation and comparison of alternative mental representations. The recruitment of precuneus areas during the generation and mental inspection and matching of alternative representations (Markowitsch et al., 2000; Kühnel et al., 2008; Hirshhorn et al., 2012) may offer an explanatory avenue for observed activations of precuneus regions not only during the RP (correct versus incorrect answering), but also during the MP (low confidence judgments versus high confidence judgments) of our study. In the latter case, it could be argued that the activation of the precuneus reflected the use of conscious visual imagery strategies, in an attempt to facilitate retrieval (Fletcher et al., 1996; Cavanna, 2007; Koriat et al., 2008; Desseilles et al., 2011).

The left MTG was found to be connected with memory recollection (Fink et al., 1996; Kroll et al., 1997; Markowitsch et al., 2000; Botzung et al., 2008; LePort et al., 2012) and essentially in the comparison between misses and correct rejections (Takahashi et al., 2008), which is reflected in the behavioral data insofar as the contrast correct versus incorrect responses was represented by correct rejections versus misses. This is supported by the importance of the medial temporal lobe in consolidation and retrieval of recently learned items (Cabeza and Nyberg, 2000; Sybirska et al., 2000; Frankland and Bontempi, 2005; Botzung et al., 2008). The observed activation of the insular cortex may reflect the posited contribution of the insula (especially of its anterodorsal part) to attentional processes, speech production, and memory recall (Manes et al., 1999; Nieuwenhuys, 2012).

Based on the current results we conjecture that a network of memory-related regions, including the hippocampus, the precuneus, areas within the posterior visual cortices (lingual gyrus), and other areas within the MTG, subserves correct (in contrast to incorrect) answering in the RP, at least at delays of around 2 h.

The contrast incorrect answering versus correct answering did not yield any significant results in our study. It can therefore be speculated that incorrect answering is not supported by a distinct neural net, but it is widely sustained by the same reconstructive approaches that support the correct answering. Incidentally, a study that investigated the neural correlates of false in comparison to true memories and vice versa via both functional connectivity analysis and direct contrasts, failed to identify any brain region displaying more activity during false versus true remembering (recollection) in direct contrasts; however, differences among the two conditions were suggested by connectivity analysis (Dennis et al., 2012).

MONITORING PROCESS (HIGH CONFIDENCE VERSUS LOW CONFIDENCE)

The factor MP (monitoring; high confidence versus low confidence) revealed no significant effect in the behavioral rating during the scanning procedure; hence there are no statistically

significant differences between responses given with high confidence and responses given with low confidence. Imaging data draw a different picture: When contrasting high subjective confidence (defined here as absolute sureness) against low confidence, activation was particularly located in the fusiform gyrus (bilaterally), the left lingual gyrus, and the left parahippocampal area (Botzung et al., 2010). One might therefore argue that absolute sureness about a given answer was to a prevailing degree elicited by the accessibility (fluency) of rich visual details during the mental recasting or recollection of episodic-like material (Wheeler et al., 2000; Greenberg and Rubin, 2003; Greenberg, 2004; Kensinger and Schacter, 2006; Daselaar et al., 2008; Addis et al., 2009; Chua et al., 2012). Greenberg (2004) remarked that "when people retrieve visual images" (p. 367) they tend to be more confident in the veracity of their memories. The activation of the fusiform gyrus has been related to the visual processing of faces (but also objects and words) and that of the parahippocampal region to place perception (Kanwisher, 2010; Hofstetter et al., 2012), processing of scenes and landmarks (Piefke et al., 2003, 2005; Sharot et al., 2007), fine grained spatial judgments (Hirshhorn et al., 2012), and reinstating of visual context to facilitate successful retrieval (Hayes et al., 2007). Furthermore, it is worth mentioning that parahippocampus and ultimately hippocampus receive a diverse gamut of synthesized sensory-specific in addition to multimodal cortical information (Nieuwenhuys et al., 2008). Faces, objects, and places were of course frequently present in the movie and consequently a common subject of the questionnaire. Incidentally, confidence effects were related to parahippocampus in a recent study by Hayes et al. (2011). In this study, in the source, but not item memory task the high versus low confidence contrast induced activation in the right hippocampus, extending to parahippocampal cortex. Furthermore left parahippocampal activations were elicited for high confidence judgments versus low confidence judgments in an fMRI study that used a modified version of the Deese-Roediger-McDermott (DRM) (Roediger III and McDermott, 1995) paradigm (Moritz et al., 2006).

In our study, the reverse contrast (low confidence versus high confidence judgments) revealed activations within the same regions and in addition a broad pattern of diffuse frontal, temporal, parietal, occipital, and limbic activation. Interestingly, other recent fMRI-studies also reported brain regions common to high and low confidence recognition, indicating the contribution of these regions to both high and low confidence recognition activity (Kim and Cabeza, 2009; Hayes et al., 2011). The recruitment of the same brain regions by both high and low confidence ratings may be due to several factors, such as a division of labor (a functional dissociation or heterogeneity) among various parts of these regions (Hofstetter et al., 2012). The widespread activation of brain regions accompanying low confidence ratings may be interpreted as reflecting processes of increased and effortful allocation of attention, executive control, searching, mental inspection, matching, and self monitoring resources.

Significant neural activity was found in our analysis in the posterior and middle cingulate cortex for low confidence judgments. This finding partly overlaps with the results of Hayes et al. (2011). In their study the posterior cingulate cortex was activated during high confidence judgments, while the middle portion of the cingulate cortex was activated during low confidence judgments. Differentiated activations within cingulate regions, concerning comparisons of high versus low confidence judgments, were also described by Chua et al. (2006). The modulation of posterior cingulate cortex by confidence judgments could be related to its converging position within the default-mode network, which enables it to integrate mnemonic information with aspects derived from internally oriented mentation, such as self-referential (e.g., self monitoring), emotional, and social information (Kim, 2013; Chua, 2012). The middle cingulate cortex has been assigned functions in response selection or decision, such deliberating in a volatile environment (Chiu et al., 2008; Frith and Frith, 2008). Huijbers et al. (2011) advanced the idea that the midcingulate cortex, supramarginal gyrus, and precuneus areas contribute to the mental inspection of competing/alternative mental representations, which may explain the activations of these areas in the low confidence condition versus high confidence condition of our study.

Henson et al. (1999) performed an event-based functional MRI study, during which they asked volunteers to make one of three judgments to each presented word during recognition. Subjects had to judge whether they recollected seeing it during study (R judgments), whether they experienced a feeling of familiarity in the absence of recollection (K judgments), or whether they did not remember seeing it during study (N judgments). The R and N judgments can be assumed to be analogical to the high and low confidence rating in this study. Henson et al. (1999) found increases for N judgments (in contrast to R judgments) in the middle and superior frontal gyrus, insula, amygdala, precuneus, inferior parietal gyrus, and MTG. Except for the amygdala exactly the same areas were found to be activated in the current study when participants rated statements with low confidence (as opposed to high confidence). It is actually easy to imagine that subjects rated a statement with low confidence when they did not remember the accordant item. With respect to amygdala some studies proposed that increased activation may be associated with increased vividness, intensity of emotional judgments and self-relevance of memory, and memory confidence (for a review see Markowitsch and Staniloiu, 2011a). In our study we did not detect amygdala activation in association with either contrast during confidence ratings. The lack of amygdala activation (Vuilleumier et al., 2004) may reflect the process of habituation, such as in blocked fMRI designs (Greenberg et al., 2005; Daselaar et al., 2008). Another interpretation could be that the modulation of amygdala by confidence judgments may vary as a function of valence (Botzung et al., 2010).

Our data suggest that confidence ratings in general modulate temporal and occipital areas, which participate to gathering and integrating information (evidence) from various perceptual/sensory areas (Kim and Cabeza, 2009; Huijbers et al., 2010). These areas may show different modulations in relationship to valence, arousal, and novelty of mnemonic information and task characteristics. Furthermore, the relation between confidence and emotional intensity may vary as a matter of valence (Botzung et al., 2010). For positively valenced visual material (movie shots) associated with high confidence, Botzung et al. (2010) found increased

activity was found in the medial temporal lobe as well as in the insula.

On the other side, specific frontal regions [inferior frontal gyrus (IFG), superior and middle frontal gyrus, paracentral lobule, precentral gyrus] were associated with low confidence in comparison to high confidence judgments, in our study, possibly reflecting executive control processes (Kim and Cabeza, 2009). The activation of the left IFG was connected to the deployment of controlled retrieval operations (Oztekin et al., 2009), especially when remembering is more difficult (Kim and Cabeza, 2009). Incidentally, the left IFG was detected to be activated in response to cues that elicit a strong need for selection among competing representations (Zhang et al., 2004; Moss et al., 2005). Furthermore higher activity at IFG was found to be correlated with higher risk aversion (Christopoulos et al., 2009) and the left IFG was attributed an essential role for suppressing prepotent, but inappropriate answers (Swick et al., 2008). One could speculate that the presence of competing mental representations may be conducive to a higher risk aversion, which may get translated into avoiding the 100% confidence option. When choosing the 50% confidence option subjects made no strong commitment and there was no risk.

Further activation during low confidence judgments was found in our study in the superior frontal gyrus being related to Brodmann area (BA) 10, which is assumed to play a role in strategic processes involved in memory retrieval and higher cognitive function (Burgess et al., 2007). This result again emphasizes the role of executive control processes in decision-making under uncertainty. We assume that when subjects are uncertain about a memory engram they invest more effort in retrieval of mnemonic information, which requires higher cognitive functions and is correlated with a rather ambivalent activation pattern compared to high confidence.

Some authors identified a laterality-confidence effect within frontal cortex. Right ventrolateral prefrontal regions were more active during low versus high confidence for both item and source memory tasks, supporting a role of this area in the processing of weak memories (Hayes et al., 2011). In the same study, several left prefrontal cortex regions showed greater activity for source than for item memory, independent of confidence.

When using a statistical height threshold of $p < 0.05$, FWE corrected for multiple comparisons only the left precuneus was activated in our study during low confidence versus high confidence ratings, a finding that mirrors results of other authors (Kim and Cabeza, 2009). Previous fMRI-studies have demonstrated that the precuneus (and posterior cingulate areas) show greater activity during recollection-based judgments (Henson et al., 1999; Wagner et al., 2005). In the study of Botzung et al. (2010) emotional intensity modulated the activity of the precuneus; furthermore, Sharot et al. (2007) found that precuneus activation correlated with the personal relevance during memory retrieval. In an elegant fMRI study that looked at the spatio-temporal dynamics of episodic-autobiographical memory, Daselaar et al. (2008) found that precuneus activation occurred at the elaboration phase of retrieval, after a specific memory had already been selected. Some authors connected the precuneus to gathering and integrating sensory details during watching movie sequences from silent films (Hasson et al., 2008). The precuneus was described as being part of the retrieval success network and was portrayed as being a sensory evidence accumulator (Huijbers et al., 2010).

In contrast to the view that holds the precuneus as being part of the retrieval success network, a recent study provided evidence that precuneus might be more implicated in retrieval confidence (decision-related retrieval processes) than successful episodic retrieval (Huijbers et al., 2010). The role of the precuneus in decision-making under uncertainty had also been suggested by Paulus et al. (2001), who asserted that both "STG and precuneus have been associated with sub processes that are consistent with the maintenance of strategies in the presence of uncertainty" (p. 97).

In conclusion, many more and differential brain areas were activated in our study when contrasting low against high confidence, a difference we attribute to greater monitoring demands and allocation of cognitive resources when confidence judgments are made under uncertainty.

CONTROL PROCESS (VOLUNTEERING VERSUS WITHHOLDING)

The factor CP (control; volunteering versus withholding) induced a significant effect in the behavioral rating during the scanning procedure: subjects rather volunteered an answer instead of withholding it, which is understandable due to the fact that each correctly volunteered answer was rewarded with a bonus, while volunteering an incorrect response led to a loss of one bonus point (moderate incentive). When no answer was provided (volunteered), no penalty or reward was instituted (no bonus points were gained or lost). The imaging data revealed differential activation for volunteering and withholding, suggesting that the two forms of behavior engage at least partially distinct sets of cognitive processes. If an answer was volunteered, particularly temporal and frontal as well as middle and posterior cingulate areas and the precuneus revealed activation. These data suggest that activation for volunteering is very similar to the neural correlates of monitoring (in contrast to retrieval). The findings are not surprising as they point to a relationship between memory confidence and answer volunteering (Koriat et al., 2008). Confidence judgments are assumed to be based on the strengths of the underlying memory trace. Also vivid remembering leads to making a high confidence decision. Volunteering an answer however might be even more influenced by perceived vividness of remembering due to the accompanying situational demands and payoffs (Belli et al., 1994; Yonelinas, 1994; Busey et al., 2000; Bradfield et al., 2002; Shaw and Zerr, 2003).

In contrast, when the answer was withheld, activations in parietal and temporal regions and also in the left caudate nucleus were identified. This may come as a surprise, because due to the task demands which were assumed to be connected with control processes like executive functioning, rather frontal and prefrontal brain activity would have been expected to reveal activation (Hedden and Gabrieli, 2010). The relevant brain areas for response inhibition which we anticipated to be related to withholding an answer include the ventrolateral PFC, mainly in the right hemisphere often in conjunction with a more extensive fronto-striato-parietal network (Garavan et al., 1999; Konishi et al., 1999; Aron et al., 2004; Walther et al., 2010; Ghahremani et al., 2012).

In our study we found during answer withholding a substantial activation in areas that play a differential role in memory retrieval

(Takahashi et al., 2008; Hoscheidt et al., 2010). This might suggest that subjects were more concentrated on the reconstruction or re-retrieval of the appropriate memory instead of response selection/inhibition (Robbins, 2007). This may have been caused by the design specification, because subjects had only very short time to answer. There might have been an overlap with the retrieval process especially when someone was not sure about the memory. We subsequently observed bilateral hippocampus activation, which speaks in favor of a great allocation of resources toward mentally reconstructing and generating internal memory details or contextual details that can be used as a retrieval cue (Koriat et al., 2008).

Caudate nuclei activity was found to be modulated by performance-feedback, including monetary rewards, with greater activation being observed during high confidence recollective experiences (Kim, 2013). However, in our study the identification of increased activation in the left caudate during withholding of answering might be congruent with new data showing the involvement of the left caudate in the inhibition of unwanted responses (Badgaiyan and Wack, 2011).

The meaning of activation of the left Heschl gyrus during withholding answers is unclear. It may reflect cognitive strategies or attempts at mental reconstruction (Zarnhofer et al., 2012). Imagining speech in third person was among other associated with left sided activation in STG and left postcentral gyrus (Shergill et al., 2001). During a visual imagery task Stokes et al. (2009) found activation of the superior temporal sulcus/Heschl's gyrus, but they speculated that it may have reflected the existence of auditory cues. Huijbers et al. (2011) however found overlapping activations in auditory cortex/ STG for auditory perception, retrieval, and imagery. The left postcentral gyrus activity was reported in one study in association with both novelty detection activity and encoding failure activity (Kim et al., 2010).

MONITORING PROCESS VERSUS RETRIEVAL PROCESS

The contrast between monitoring and retrieval resulted in temporal, occipital, parietal, and frontal brain activation, and moreover bilateral activation of the precuneus and differential left cingulate cortex areas. While during the RP subjects rated each statement as correct or incorrect, the MP was defined as a confidence judgment. During the confidence judgment, subjects monitored their recognition decision, and made an explicit subjective judgment about their previous memory performance. It is common sense to make the assumption that both processes (RP and MP) are related, although experience shows that there are instances where subjective confidence and objective correctness of memory answers divert (Simons et al., 2010). As Chua et al. (2009) expounded, confidence judgments are considered to be based on the strength and/or quality of the underlying memory trace, ease of retrieval, and also on study specific heuristics and test conditions, and ultimately on participants' general mnemonic abilities (Belli et al., 1994; Yonelinas, 1994; Busey et al., 2000; Bradfield et al., 2002; Shaw and Zerr, 2003). The functional imaging study conducted by Moritz et al. (2006) reported an increase in confidence at recognition associated with bilateral activation in the anterior and posterior cingulate cortex along with medial temporal regions. In comparison to recognition judgments, confidence judgments induced higher activations in various regions (such as superior frontal, dorsomedial frontal, orbitofrontal, and lateral parietal cortices), including areas involved in self-referential processing and internal mentation (such as medial prefrontal cortex) in an fMRI study conducted by Chua et al. (2006). Our own results reveal that, when contrasting confidence judgments to retrieval, activations are detected in areas involved in generation and inspection of mental imagery (e.g., precuneus, middle frontal gyrus, middle cingulate gyrus, supramarginal gyrus; Huijbers et al., 2011; Hirshhorn et al., 2012), monitoring and detecting conflict [e.g., anterior cingulate cortex (Acc)], post-retrieval monitoring and verification (prefrontal areas), decision and response selection under uncertainty (e.g., middle cingulate cortex, Frith and Frith, 2008), cognitive dissonance (e.g., Acc; van Veen et al., 2009), self appraisal (e.g., medial prefrontal cortex areas, Ries et al., 2012), and motivation and emotional processing (e.g., Acc). Activation of the Acc may support the relationship between monitoring processes and executive functions, given that the dorsal part of the Acc is connected with the prefrontal cortex, which plays a crucial role in executive functioning. Incidentally, Fan et al. (2005) described a kind of executive control network that showed activation of the anterior cingulate along with other brain areas.

The reverse contrast (RP versus CP) did not yield any statistically significant difference in our study. One may conclude from this that, even though monitoring and retrieval processes are strongly connected with each other, the former is characterized by a higher demand for cognitive performance and an additional allocation of resources toward internal reflection, inspection, verification, and comparison of alternatives and self-referential processing (Chua, 2012).

CONTROL PROCESS VERSUS RETRIEVAL PROCESS

According to our results, the CP (in contrast to retrieval) revealed (amongst others) the same neural activation as monitoring (in contrast to retrieval), namely the left MTG and the middle frontal gyrus. The left MTG was found to be activated during episodic-autobiographical memory retrieval (Markowitsch et al., 2000), but also during a variety of semantic tasks (for a review, see Svoboda et al., 2006). The MTG is indeed portrayed as an information convergence hub, as it integrates auditory and visual information (Visser et al., 2012). The left MTG is considered to be a crucial node of the conceptual network and has been attributed roles in word-picture matching, mapping concepts to words, and semantic task decision. Its recruitment during retrieval of old episodic memories was conjectured to support the idea of multimodal representation of episodic memory (Fink et al., 1996), on one hand and the more complex and effortful process of ecphorizing, on the other hand (Markowitsch et al., 2000). As mentioned above the left MTG was found to be activated during correct answering versus incorrect responding during the RP (Takahashi et al., 2008), which is in line with its involvement in the monitoring and CP, however the outcome of both processes is based on recognition decision (Chua et al., 2009).

MEMORY ACCURACY

The factor MAC (high MAC versus low MAC) induced differential brain activation for both contrasts. High MAC was here defined

as withholding an incorrect answer in contrast to volunteering an incorrect answer. The present neural activation related to MAC (in contrast to inaccuracy) again confirms our previous assumption of a network of memory-related areas including the hippocampus, the precuneus, and the MTG being related to correct (in contrast to incorrect) memory retrieval hence these areas showed activation. The important role of the medial temporal lobe (including the parahippocampal gyrus) in memory performance and, particularly in non-verbal memory, has been known since the mid-1950s (Scoville and Milner, 2000; Frankland and Bontempi, 2005).

The reverse contrast, low MAC (in contrast to high MAC), was defined as volunteering incorrect answers. Interestingly, only the left superior frontal gyrus and the left insula demonstrated neural activation during low MAC in comparison to the high MAC condition. Mohr and colleagues investigated the role of the insula, concluding that this region was consistently associated with risky behavior (Weller et al., 2009; Mohr et al., 2010). Moreover the insula was found to be predominantly active in the presence of potential losses (Mohr et al., 2010). Insular activations were also reported in relationships to unexpected outcomes and errors (Klein et al., 2013). Low accuracy was defined in our study as volunteering an incorrect answer. If an answer rated with a confidence less that 100 percent were ventured, subjects would experience a homeostatic and visceral change in the face of potential losses, which would lead to insula activations. This would be in accordance with our experimental design hence participants knew that incorrect decisions would result in a loss of bonus and moreover therewith tended to a risky decision. Early studies had shown that people are loss aversive; however newer data pointed to a reduction (or even reversal of loss aversion) if people anticipate gains and losses and the anticipated loss is small (Harinck et al., 2007). The activation of the left superior frontal gyrus was detected in an imaging study when contrasting conceptual false to conceptual true information (Garoff-Eaton et al., 2007). In another study, activations of superior frontal gyri were reported to signify loss aversion when making decisions under risk (Tom et al., 2007; Xu et al., 2009). In our study the left superior frontal gyrus was also modulated when contrasting low confidence with high confidence ratings. It is therefore possible that uncertainty and inaccuracy belong to related processes.

CONCLUSION

In a 7 Tesla fMRI study that adopted the paradigm developed by Koriat and Goldsmith (1996a,b) and used complex, emotional, naturalistic, and culturally appropriate material at encoding (the movie "The New Cat"), we have provided evidence for common and unique neural correlates underlying the processes of memory retrieval, monitoring and control, and MAC performance in a group of healthy young adults. The participants were well matched for educational background and neuropsychological performance and equally distributed with respect to sex. The administration of the memory queries about the movie, which took place after a period of interference of about 2 h, tried to approximate the real-life situations related to eyewitness testimony. The 2-h period between seeing the short movie and being tested in the scanner was completely filled by neuropsychological testing and pre-scanning procedure; therefore the participants had no possibility to recapitulate details or to talk about the film. Furthermore, as it was mentioned above the participants were not informed that their memory of the movie would be probed later – a condition that again tried to approximate real-life eyewitness testimony circumstances.

As expected, the correct answering versus incorrect responding in the RP was accompanied by increased activation in hippocampus (Habib and Nyberg, 2008). The material used for incidental encoding involved complex multisensory information and it is known that information coming from all sensory modalities is transmitted to the hippocampal formation. In our study, we found a left lateralization of hippocampal engagement; this finding is relevant given data supporting the involvement of the left hippocampus during the retrieval of strict episodic memories in response to a specific cue.

Strict episodic memories are characterized by increased vividness, perceptual details, emotional engagement, self-relevance, and autonoetic consciousness (Markowitsch and Staniloiu, 2011b, 2012). The latter entails mental time traveling and reliving of the contextual details from the time of the encoding.

An alternative explanation is that the left hippocampal activation during correct answers (in comparison to incorrect answers) may have indicated a correct rejection of novel, unstudied material (either the detection/encoding of new material or a recollection rejection strategy). In our study, subjects gave more correct than incorrect answers, however, this was in general a consequence of correct rejection (instead of a hit) (McDonough and Gallo, 2012). The left hippocampus was also modulated in our study during the contrast high MAC versus low MAC.

One can assume from the results related to monitoring processes that temporal areas are involved in confidence ratings in general, whereas particular frontal regions are associated with low confidence judgments. The activation of the parahippocampal gyrus during confidence memory ratings is congruent with data showing that, similarly to hippocampus, parahippocampus receives a large gamut of sensory-specific and multimodal cortical information. The parahippocampus has been involved in retrieving non-verbal material and other authors evidenced its activation in relation to confidence memory judgments (Hayes et al., 2011). The finding of a significant positive association between left precuneus activation and the contrast low confidence versus high confidence judgments is consistent with other reports pointing to the recruitment of precuneus areas during post-retrieval monitoring processes (Huijbers et al., 2010).

In our study, answer volunteering seemed to be subject to increased monitoring processes, in contrast to answer withholding. These monitoring processes (suggested by activations in prefrontal, cingulate, and parietal cortices) may be modulated by the amount of potential gain relative to loss.

The increased bilateral hippocampal activation associated with withholding answers may reflect the posited role of hippocampus in disambiguation, mental construction, prospection, and future-minded choices (Ross et al., 2009; Peters and Büchel, 2010). As withholding of information may represent low memory confidence and/or reduced memory vividness, there may be a need for inter-hemispheric engagement of hippocampal formation, in

order to generate and bind together pieces of information that are sensorially varied and complex (Botzung et al., 2010).

The caudate nuclei, which are part of the reward system, are assumed to support satisfaction linked to target detection (especially in relationship to hits) (Kim, 2013), monetary gain, and acquisition of good reputation (Izuma et al., 2008). In our study, we only found a left caudate activation during withholding of answering, but we interpreted this differently, namely by relating it to the involvement of the left caudate in the inhibition of unwanted responses (Badgaiyan and Wack, 2011).

The present study has a number of limitations; therefore its results cannot be generalized to the complex eyewitness situations. The short emotional movie only established a bridge between old laboratory memory testing and real-life situations, by inducing a controlled experience, with elements of real-life events (Mendelsohn et al., 2010). In real life, a much more variable mismatch between encoding situations and conditions at the time of memory testing might exist. The delay between learning and testing was about 2 h in our study. In eyewitness testimony situations, variable delays might be encountered. The observed neural correlates associated with some of the processes described above might not hold true at longer testing delays (Schacter and Loftus, 2013). A higher degree of homogeneity characterized the population investigated in our study, which obviously is not the case in eyewitness cases. Furthermore, we used a modest incentive during the CP of our study, whereas higher incentives may be involved in eyewitness testimony settings.

Despite its limitations, the present study demonstrates that dissociation between the retrieval, monitoring, and control processes described by the paradigm of Koriat and Goldsmith is realizable at the neurobiological level. We found a network of memory-related regions, including the hippocampus, the precuneus, and the MTG playing a crucial role in correct memory retrieval (correct answering during the RP) and MAC. Moreover, we show evidence for the fact that volunteering may be connected with monitoring processes hence both seem to be based on the strengths of the accordant memory trace. Our results reveal a strong relationship between monitoring and retrieval processes, whereas monitoring is defined by a higher demand for cognitive performance.

Beyond that, monitoring and control processes have in common that their outcome is based on a recognition decision which reflects their strong connection to memory retrieval – this relation seems to be mediated by activation of the medial temporal gyrus.

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REFERENCES

Addis, D. R., Knapp, K., Roberts, R. P., and Schacter, D. L. (2012). Routes to the past: neural substrates of direct and generative autobiographical memory retrieval. *Neuroimage* 59, 2908–2922.

Addis, D. R., Pan, L., Vu, M. A., Laiser, N., and Schacter, D. L. (2009). Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imagining and remembering. *Neuropsychologia* 47, 2222–2238.

Aron, A. R., Robbins, T. W., and Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn. Sci. (Regul. Ed.)* 8, 170–177.

Badgaiyan, R. D., and Wack, D. (2011). Evidence of dopaminergic processing of executive inhibition. *PLoS ONE* 6:e28075. doi:10.1371/journal.pone.0028075

Beck, A. T., Steer, R. A., and Hautzinger, M. (1995). *Beck-Depressions-Inventar (BDI)*. Bern: Hans Huber.

Belli, R. F., Lindsay, D. S., Gales, M. S., and McCarthy, T. T. (1994). Memory impairment and source misattribution in postevent misinformation experiments with short retention intervals. *Mem. Cognit.* 22, 40–54.

Botzung, A., Denkova, E., Ciuciu, P., Scheiber, C., and Manning, L. (2008). The neural bases of the constructive nature of autobiographical memories studied with a self-paced fMRI design. *Memory* 16, 351–363.

Botzung, A., Rubin, D. C., Miles, A., Cabeza, R., and LaBar, K. S. (2010). Mental hoop diaries: emotional memories of a college basketball game in rival fans. *J. Neurosci.* 30, 2130–2137.

Bradfield, A. L., Wells, G. L., and Olson, E. A. (2002). The damaging effect of confirming feedback on the relation between eyewitness certainty and identification accuracy. *Mem. Cognit.* 87, 112–120.

Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J., and Markowitsch, H. J. (2005). Decision-making deficits of Korsakoff patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology* 19, 267–277.

Brand, M., and Markowitsch, H. J. (2010). Mechanisms contributing to decision-making difficulties in late adulthood: theoretical approaches, speculations and empirical evidence. *Gerontology* 56, 435–440.

Brickenkamp, R., and Zillmer, E. (1998). *The d2 Test of Attention*. Seattle, WA: Hogrefe and Huber.

Burgess, P. W., Gilbert, S. J., and Dumontheil, I. (2007). Function and localization within rostral prefrontal cortex (area 10). *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 887–899.

Busey, T. A., Tunnicliff, J., Loftus, G. R., and Loftus, E. F. (2000). Accounts of the confidence-accuracy relation in recognition memory. *Psychon. Bull. Rev.* 7, 26–48.

Cabeza, R., and Nyberg, L. (2000). Neural bases of learning and memory: functional neuroimaging evidence. *Curr. Opin. Neurol.* 13, 415–421.

Cavanna, A. E. (2007). The precuneus and consciousness. *CNS Spectr.* 12, 545–552.

Cavanna, A. E., and Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583.

Chiu, P. H., Kavali, M. A., Kishida, K. T., Tomlin, D., Klinger, L. G., Klinger, M. R., et al. (2008). Self responses along cingulate cortex reveal quantitative neural phenotype for high-functioning autism. *Neuron* 57, 463–473.

Christopoulos, G. I., Tobler, P. N., Bossaerts, P., Dolan, R. J., and Schultz, W. (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *J. Neurosci.* 29, 12574–12583.

Chua, E. F. (2012). "Evaluating confidence in our memories," in *Memory and Law*, eds L. Nadel and W. P. Sinnott-Armstrong (New York: Oxford University Press), 119–141.

Chua, E. F., Hannula, D. E., and Ranganath, C. (2012). Distinguishing highly confident accurate and inaccurate memory: insights about relevant and irrelevant influences on memory confidence. *Memory* 20, 48–62.

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., and Sperling, R. A. (2006). Understanding metamemory: neural correlates of the cognitive process and subjective level of confidence in recognition memory. *Neuroimage* 29, 1150–1160.

Chua, E. F., Schacter, D. L., and Sperling, R. A. (2009). Neural correlates of metamemory: a comparison of feeling-of-knowing and retrospective confidence judgments. *J. Cogn. Neurosci.* 21, 1751–1765.

Daselaar, S. M., Rice, H. J., Greenberg, D. L., Cabeza, R., LaBar, K. S., and Rubin, D. C. (2008). The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. *Cereb. Cortex* 18, 217–229.

De Mulder, R. V., van Noortwijk, K., Goldsmith, M., Pansky, A., Koriat, A., and Labin, S. K. (2010). CORMAS: a computerized tool for the analysis of eyewitness memory correspondence. *Eur. J. Law Technol.* 1. Available at: http://ejlt.org//article/view/34/72

Dennis, N. A., Bowman, C. R., and Vandekar, S. N. (2012). True and phantom recollection: an fMRI investigation of similar and distinct neural correlates and connectivity. *Neuroimage* 59, 2982–2993.

Derogatis, L. R. (1993). *BSI: Brief Symptom Inventory*. Minneapolis: National Computer Systems.

Desseilles, M., Dang-Vu, T. T., Sterpenich, V., and Schwartz, S. (2011). Cognitive and emotional processes during dreaming: a neuroimaging view. *Conscious. Cogn.* 20, 998–1008.

Dörfel, D., Werner, A., Schaefer, M., von Kummer, R., and Karl, A. (2009). Distinct brain networks in recognition memory share a defined region in the precuneus. *Eur. J. Neurosci.* 30, 1947–1959.

Düzel, E., Habib, R., Rotte, M., Guderian, S., Tulving, E., and Heinze, H. J. (2003). Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. *J. Neurosci.* 23, 9439–9444.

Fahrenberg, J., Hampel, R., and Selg, H. (2001). *Freiburger Persönlichkeitsinventar (FPI-R) [Freiburger Personality Inventory]*. Göttingen: Hogrefe.

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., and Posner, M. I. (2005). The activation of attentional networks. *Neuroimage* 26, 471–479.

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., and Heiss, W.-D. (1996). Cerebral representation of one's own past: neural networks involved in autobiographical memory. *J. Neurosci.* 16, 4275–4282.

Fletcher, P. C., Frith, C. D., Baker, S. C., Shallice, T., Frackowiak, R. S., and Dolan, R. J. (1995). The mind's eye -precuneus activation in memory related imagery. *Neuroimage* 2, 195–200.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S., and Dolan, R. J. (1996). Brain activity during memory retrieval. The influence of imagery and semantic cueing. *Brain* 119, 1587–1596.

Frankland, P. W., and Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130.

Friedman, D., Nessler, D., Kulik, J., and Hamberger, M. (2011). The brain's orienting response (novelty P3) in patients with unilateral temporal lobe resections. *Neuropsychologia* 49, 3474–3483.

Frisk, V., and Milner, B. (1990). The role of the left hippocampal region in the acquisition and retention of story content. *Neuropsychologia* 28, 349–359.

Frith, C. D., and Frith, U. (2008). The self and its reputation in autism. *Neuron* 57, 331–332.

Gallo, D. A. (2011). "Distinctiveness and the law of false recollection suppression," in *Abstracts of the 5th International Conference on Memory S423* (York: University of York), 95.

Gallo, D. A., Meadow, N. G., Johnson, E. L., and Foster, K. T. (2008). Deep levels of processing elicit a distinctiveness heuristic: evidence from the criterial recollection task. *J. Mem. Lang.* 58, 1095–1111.

Garavan, H., Ross, T. J., and Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proc. Natl. Acad. Sci. U.S.A.* 96, 8301–8306.

Garoff-Eaton, R. J., Kensinger, E. A., and Schacter, D. L. (2007). The neural correlates of conceptual and perceptual false recognition. *Learn. Mem.* 14, 684–692.

Ghahremani, D. G., Lee, B., Robertson, C. L., Tabibria, G., Morgan, A. T., De Shetler, N., et al. (2012). Striatal dopamine D_2/D_3 receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J. Neurosci.* 32, 7316–7324.

Gilboa, A., Winocur, G., Grady, C. L., Hevenor, S. J., and Moscovitch, M. (2004). Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. *Cereb. Cortex* 14, 1214–1225.

Gilboa, A., Winocur, G., Rosenbaum, R. S., Poreh, A., Gao, F., Black, S. E., et al. (2006). Hippocampal contributions to recollection in retrograde and anterograde amnesia. *Hippocampus* 16, 966–980.

Goldsmith, M., Koriat, A., and Weinberg-Eliezer, A. (2002). Strategic regulation of grain size in memory reporting. *J. Exp. Psychol. Gen.* 131, 73–95.

Greenberg, D. L. (2004). President Bush's false 'flashbulb' memory of 9/11/01. *Appl. Cogn. Psychol.* 18, 363–370.

Greenberg, D. L., Rice, J. J., Cabeza, R., Rubin, D. C., and Labar, K. S. (2005). Co-activation of the amygdala, hippocampus, and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia* 43, 659–674.

Greenberg, D. L., and Rubin, D. C. (2003). The neuropsychology of autobiographical memory. *Cortex* 39, 687–728.

Greve, A., Doidge, A. N., Evans, C. J., and Wilding, E. L. (2010). Functional neuroanatomy supporting judgments of when events occurred. *J. Neurosci.* 30, 7099–7104.

Gruneberg, M. M., and Morris, P. (eds). (1978). *Aspects of Memory*. London: Methuen.

Habib, R., and Nyberg, L. (2008). Neural correlates of availability and accessibility in memory. *Cereb. Cortex* 18, 1720–1726.

Halamish, V., Goldsmith, M., and Jacoby, L. L. (2012). Source-constrained recall: front-end and back-end control of retrieval quality. *J. Exp. Psychol. Learn. Mem. Cogn.* 38, 1–15.

Harinck, F., Van Dijk, E., Van Beest, I., and Mersmann, P. (2007). When gains loom larger than losses: reversed loss aversion for small amounts of money. *Psychol. Sci.* 18, 1099–1105.

Härting, C., Markowitsch, H. J., Neufeld, H., Calabrese, P., Deisinger, K., and Kessler, J. (2000). *Die Wechsler-Memory-Scale Revised. Deutschsprachige Adaptation*. Bern: Huber.

Hashimoto, R., Abe, N., Ueno, A., Fujii, T., Takahashi, S., and Mori, E. (2012). Changing the criteria for old/new recognition judgments can modulate activity in the anterior hippocampus. *Hippocampus* 22, 141–148.

Hasson, U., Yang, E., Vallines, I., Heeger, D. J., and Rubin, N. (2008). A hierarchy of temporal receptive windows in human cortex. *J. Neurosci.* 28, 2539–2550.

Hayes, S. M., Buchler, N., Stokes, J., Kragel, J., and Cabeza, R. (2011). Neural correlates of confidence during item recognition and source memory retrieval: evidence for both dual-process and strength memory theories. *J. Cogn. Neurosci.* 23, 3959–3971.

Hayes, S. M., Nadel. L., and Ryan, L. (2007). The effect of scene context on episodic object recognition: parahippocampal cortex mediates memory encoding and retrieval success. *Hippocampus* 17, 873–889.

Hedden, T., and Gabrieli, J. D. E. (2010). Shared and selective neural correlates of inhibition, facilitation, and shifting processes during executive control. *Neuroimage* 51, 421–431.

Helmstaedter, C., Lendt, M., and Lux, S. (2001). *VLMT–Verbaler Lern- und Merkfähigkeitstest*. Göttingen: Beltz Test GmbH.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., and Dolan, R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J. Neurosci.* 19, 3962–3972.

Herrmann, D. J., McEvoy, C., Hertzog, C., Hertel, V. J., and Johnson, M. K. (eds) (1996). *Basic and Applied Memory Research: Practical Applications*. Hillsdale: Erlbaum.

Hirshhorn, M., Grady, C., Rosenbaum, R. S., Winocur, G., and Moscovitch, M. (2012). Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: an fMRI study. *Neuropsychologia* 50, 3094–3106.

Hofstetter, C., Achaibou, A., and Vuilleumier, P. (2012). Reactivation of visual cortex during memory retrieval: content specificity and emotional modulation. *Neuroimage* 60, 1734–1745.

Horn, W. (1983). *Leistungsprüf System*, 2nd Edn. Göttingen: Hogrefe.

Hoscheidt, S. M., Nadel, L., Payne, J., and Ryan, L. (2010). Hippocampal activation during retrieval of spatial context from episodic and semantic memory. *Behav. Brain Res.* 212, 121–132.

Huijbers, W., Pennartz, C. M., and Daselaar, S. M. (2010). Dissociating the "retrieval success" regions of the brain: effects of retrieval delay. *Neuropsychologia* 48, 491–497.

Huijbers, W., Pennartz, C. M., Rubin, D. C., and Daselaar, S. M. (2011). Imagery and retrieval of auditory and visual information: neural correlates of successful and unsuccessful performance. *Neuropsychologia* 49, 1730–1740.

Izuma, K., Saito, D. N., and Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron* 58, 284–294.

Kafkas, A., and Montaldi, D. (2012). Familiarity and recollection produce distinct eye movement, pupil and medial temporal lobe responses when memory strength is matched. *Neuropsychologia* 50, 3080–3093.

Kanwisher, N. (2010). Functional specificity in the human brain: a window into the functional architecture of the mind. *Proc. Natl. Acad. Sci. U.S.A.* 107, 11163–11170.

Kelley, C. M., and Sahakyan, L. (2003). Memory, monitoring, and control in the attainment of memory accuracy. *J. Mem. Lang.* 48, 704–721.

Kensinger, E. A., and Schacter, D. L. (2006). Neural processes underlying memory attribution on a reality-monitoring task. *Cereb. Cortex* 16, 1126–1133.

Kim, H. (2013). Differential neural activity in the recognition of old versus new events: an activation likelihood estimation meta-analysis. *Hum. Brain Mapp.* 34, 814–836.

Kim, H., and Cabeza, R. (2009). Common and specific brain regions in high- versus low-confidence recognition memory. *Brain Res.* 28, 103–113.

Kim, H., Daselaar, S. H., and Cabeza, R. (2010). Overlapping brain activity between episodic memory encoding and retrieval: roles of the task-positive and task-.negative networks. *Neuroimage* 49, 145–154.

Klatzky, R. L., and Erdelyi, M. H. (1985). The response criterion problem in tests of hypnosis and memory. *Int. J. Clin. Exp. Hypn.* 33, 246–257.

Klein, T. A., Ullsperger, M., and Danielmeier, C. (2013). Error awareness and the insula: links to neurological and psychiatric diseases. *Front. Hum. Neurosci.* 7:14. doi:10.3389/fnhum.2013.00014

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., and Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* 122, 981–991.

Koriat, A., and Goldsmith, M. (1994). Memory in naturalistic and laboratory contexts: distinguishing the accuracy-oriented and quantity-oriented approaches to memory assessment. *J. Exp. Psychol. Gen.* 123, 297–315.

Koriat, A., and Goldsmith, M. (1996a). Memory metaphors and the real-life/laboratory controversy: correspondence versus storehouse conceptions of memory. *Behav. Brain Sci.* 19, 167–228.

Koriat, A., and Goldsmith, M. (1996b). Monitoring and control processes in the strategic regulation of memory accuracy. *Psychol. Rev.* 103, 490–517.

Koriat, A., Goldsmith, M., and Halamish, V. (2008). "Controlled processes in voluntary remembering," in *Cognitive Psychology of Memory*, ed. H. L. Roediger, III (Oxford: Elsevier), 307–324.

Koriat, A., Goldsmith, M., and Painsky, A. (2000). Toward a psychology of memory accuracy. *Annu. Rev. Psychol.* 51, 481–537.

Kroll, N., Markowitsch, H. J., Knight, R., and von Cramon, D. Y. (1997). Retrieval of old memories – the temporo-frontal hypothesis. *Brain* 120, 1377–1399.

Kühnel, S., Woermann, F. G., Mertens, M., and Markowitsch, H. J. (2008). Involvement of the orbitofrontal cortex during correct and false recognitions of visual stimuli. Implications for eyewitness decisions on an fMRI study using a film paradigm. *Brain Imaging Behav.* 2, 163–176.

Leding, J. K. (2012). Working memory predicts the rejection of false memories. *Memory* 20, 217–223.

LePort, A. K., Mattfeld, A. T., Dickinson-Anson, H., Fallon, J. H., Stark, C. E., Kruggel, F., et al. (2012). Behavioral and neuroanatomical investigation of Highly Superior Autobiographical Memory (HSAM). *Neurobiol. Learn. Mem.* 98, 78–92.

Leshikar, E. D., Duarte, A., and Hertzog, C. (2012). Task-selective memory effects for successfully implemented encoding strategies. *PLoS ONE* 7:e38160. doi:10.1371/journal.pone.0038160

Lezak, M. D. (1995). *Neuropsychological Assessment*, 3rd Edn. New York: Oxford University Press.

Manes, F., Paradiso, S., and Robinson, R. G. (1999). Neuropsychiatric effects of insular stroke. *J. Nerv. Ment. Dis.* 187, 707–712.

Markowitsch, H. J. (1994). The memory storehouse. *Trends Neurosci.* 17, 513–514.

Markowitsch, H. J. (2008). "Anterograde amnesia," in *Handbook of Clinical Neurology*, 3rd Edn, ed. G. M. B. L. Goldenberg (New York: Elsevier), 155–183.

Markowitsch, H. J., and Staniloiu, A. (2011a). Amygdala in action: relaying biological and social significance to autobiographic memory. *Neuropsychologia* 49, 718–733.

Markowitsch, H. J., and Staniloiu, A. (2011b). Memory, autonoetic consciousness, and the self. *Conscious. Cogn.* 20, 16–39.

Markowitsch, H. J., and Staniloiu, A. (2012). Amnesic disorders. *Lancet* 380, 1429–1440.

Markowitsch, H. J., Thiel, A., Reinkemeier, M., Kessler, J., Koyuncu, A., and Heiss, W. D. (2000). Right amygdalar and temporofrontal activation during autobiographic, but not during fictitious memory retrieval. *Behav. Neurol.* 12, 181–190.

McDonough, I. M., and Gallo, D. A. (2012). Illusory expectations can affect retrieval-monitoring accuracy. *J. Exp. Psychol. Learn. Mem. Cogn.* 38, 391–404.

Mendelsohn, A., Furman, O., and Dudai, Y. (2010). Signatures of memory: brain coactivations during retrieval distinguish correct from incorrect recollection. *Front. Behav. Neurosci.* 4:18. doi:10.3389/fnbeh.2010.00018

Mohr, P. N. C., Biele, G., and Heekeren, H. R. (2010). Neural processing of risk. *J. Neurosci.* 30, 6613–6619.

Moritz, S., Gläscher, J., Sommer, T., Büchel, C., and Braus, D. F. (2006). Neural correlates of memory confidence. *Neuroimage* 33, 1188–1193.

Moss, H. E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., et al. (2005). Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. *Cereb. Cortex* 15, 1723–1735.

Nieuwenhuys, R. (2012). The insular cortex. *Prog. Brain Res.* 195, 123–163.

Nieuwenhuys, R., Voogd, J., and van Hujzen, C. (2008). *The Human Central Nervous System*, 4th Edn. Berlin: Springer.

Nyberg, L., Habib, R., McIntosh, A. R., and Tulving, E. (2000). Reactivation of encoding-related brain activity during memory retrieval. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11120–11124.

Oddo, S., Lux, S., Weiss, P. H., Schwab, A., Welzer, H., Markowitsch, H. J., et al. (2010). Specific role of medial prefrontal cortex in retrieving recent autobiographical memories: an fMRI study of young female subjects. *Cortex* 46, 29–39.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.

Oztekin, I., Curtis, C. E., and McElree, B. (2009). The medial temporal lobe and the left inferior prefrontal cortex jointly support interference resolution in verbal working memory. *J. Cogn. Neurosci.* 21, 1967–1979.

Pansky, A., and Tenenboim, E. (2011). Inoculating against eyewitness suggestibility via interpolated verbatim vs. gist testing. *Mem. Cognit.* 39, 155–170.

Paulus, M. P., Hozack, N., Zauscher, B., McDowell, J. E., Frank, L., Brown, G. G., et al. (2001). Prefrontal, parietal, and temporal cortex networks underlie decision-making in the presence of uncertainty. *Neuroimage* 13, 91–100.

Peters, J., and Büchel, C. (2010). Episodic future thinking reduces rewards delay discounting through an enhancement of prefrontal-mediotemporal interactions. *Neuron* 65, 138–148.

Piefke, M., Weiss, P. H., Markowitsch, H. J., and Fink, G. R. (2005). Gender differences in the functional neuroanatomy of emotional episodic autobiographical memory. *Hum. Brain Mapp.* 24, 313–324.

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., and Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain* 126, 850–868.

Poppenk, J., Walia, G., McIntosh, A. R., Joanisse, M. F., Klein, D., and Kohler, S. (2008). Why is the meaning of a sentence better remembered than its form? An fMRI study on the role of novelty-encoding processes. *Hippocampus* 18, 909–918.

Poser, B. A., Koopmans, P. J., Witzel, T., Wald, L. L., and Barth, M. (2010). Three dimensional echo-planar imaging at 7 Tesla. *Neuroimage* 51, 261–266.

Poser, B. A., and Norris, D. G. (2009). Investigating the benefits of multi-echo EPI for fMRI at 7 T. *Neuroimage* 45, 1162–1172.

Ries, M. L., McLaren, D. G., Bendlin, B. B., Guanfan, X., Rowley, H. A., Birn, R., et al. (2012). Medial prefrontal functional connectivity – relation to memory self-appraisal accuracy in older adults with and without memory disorders. *Neuropsychologia* 50, 603–611.

Robbins, T. W. (2007). Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 917–932.

Roediger, H. L. III, and McDermott, K. B. (1995). Creating false memories: remembering words not presented on lists. *J. Exp. Psychol. Learn. Mem. Cogn.* 21, 803–814.

Roediger, H. L. (1980). Memory metaphors in cognitive psychology. *Mem. Cognit.* 8, 231–246.

Ross, R. S., Brown, T. I., and Stern, C. E. (2009). The retrieval of learned sequences engages the hippocampus: evidence from fMRI. *Hippocampus* 19, 790–799.

Rutishauser, U., Schuman, E. M., and Mamelak, A. N. (2008). Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. *Proc. Natl. Acad. Sci. U.S.A.* 105, 329–334.

Schacter, D. L., Israel, L., and Racine, C. (1999). Suppressing false recognition in younger and older adults:

the distinctiveness heuristic. *J. Mem. Lang.* 40, 1–24.
Schacter, D. L., and Loftus, E. F. (2013). Memory and law: what can cognitive neuroscience contribute? *Nat. Neurosci.* 16, 119–123.
Scoville, W. B., and Milner, B. (2000). Loss of recent memory after bilateral hippocampal lesions. 1957. *J. Neuropsychiatry Clin. Neurosci.* 12, 103–113.
Sharot, T., Martorella, E. A., Delgado, M. R., and Phelps, E. A. (2007). How personal experience modulates the neural circuitry of memories of September 11. *Proc. Natl. Acad. Sci. U.S.A.* 104, 389–394.
Shaw, J. S., and Zerr, T. K. (2003). Extra effort during memory retrieval may be associated with increases in eyewitness confidence. *Law Hum. Behav.* 27, 315–329.
Shergill, S., Bullmore, E. T., Brammer, M. J., Williams, S. C., Murray, R. M., and McGuire, P. K. (2001). A functional study of auditory verbal imagery. *Psychol. Med.* 31, 241–253.
Simons, J. S., Peers, P. V., Mazuz, Y. S., Berryhill, M. E., and Olson, I. R. (2010). Dissociation between memory accuracy and memory confidence following bilateral parietal lesions. *Cereb. Cortex* 20, 479–485.
Stokes, M., Thompson, R., Cusack, R., and Duncan, J. (2009). Top-down activation of shape-specific population codes in visual cortex during mental imagery. *J. Neurosci.* 29, 1565–1572.
Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208.
Swick, D., Ashley, V., and Turken, A. U. (2008). Left inferior frontal gyrus is critical for response inhibition. *BMC Neurosci.* 9:102. doi:10.1186/1471-2202-9-102
Sybirska, E., Davachi, L., and Goldman-Rakic, P. S. (2000). Prominence of direct entorhinal-CA1 pathway activation in sensorimotor and cognitive tasks revealed by 2-DG functional mapping in nonhuman primate. *J. Neurosci.* 20, 5827–5834.
Takahashi, E., Kenichi, O., and Kim, D. S. (2008). Dissociated pathways for successful memory retrieval from the human parietal cortex: anatomical and functional connectivity analyses. *Cereb. Cortex* 18, 1771–1778.
Tom, S. M., Fox, C. R., Trepel, C., and Poldrack, R. A. (2007). The neural basis of loss aversion in decision-making under risk. *Science* 315, 515–518.
Tulving, E., Markowitsch, H. J., Kapur, S., Habib, R., and Houle, S. (1994). Novelty encoding networks in the human brain: data from positron emission tomography studies. *Neuroreport* 5, 2525–2528.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2, 273–289.
van Veen, V., Krug, M. K., Schooler, J. W., and Carter, C. S. (2009). Neural activity predicts attitude change in cognitive dissonance. *Nat. Neurosci.* 12, 1469–1474.
Viard, A., Desgranges, B., Eustache, F., and Piolino, P. (2012). Factors affecting medial temporal lobe engagement for past and future episodic events: an ALE meta-analysis of neuroimaging studies. *Brain Cogn.* 80, 111–125.
Visser, M., Jefferies, E., Embleton, K. V., and Lambon Ralph, M. A. (2012). Both the middle temporal gyrus and the ventral anterior temporal area are crucial for multimodal semantic processing: distortion-corrected fMRI evidence for a double gradient of information convergence in the temporal lobes. *J. Cogn. Neurosci.* 24, 1766–1778.
Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* 7, 1271–1278.
Wagner, A. D., Shannon, B. J., Kahn, I., and Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn. Sci. (Regul. Ed.)* 9, 445–453.
Walther, S., Goya-Maldonado, R., Stippich, C., Weisbrod, M., and Kaiser, S. (2010). A supramodal network for response inhibition. *Neuroreport* 21, 191–195.
Weller, J. A., Levin, I. P., Shiv, B., and Bechara, A. (2009). The effects of insula damage on decision–making for risky gains and losses. *Soc. Neurosci.* 4, 347–358.
Wheeler, M. E., Petersen, S. E., and Buckner, R. L. (2000). Memory's echo: vivid remembering reactivates sensory-specific cortex. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11125–11129.
Wixted, J. T., and Squire, L. R. (2011). The familiarity/recollection distinction does not illuminate medial temporal lobe function: response to Montaldi and Mayes. *Trends Cogn. Sci. (Regul. Ed.)* 15, 340–341.
Xu, L., Liang, Z. Y., Wang, K., Li, S., and Jiang, T. (2009). Neural mechanism of intertemporal choice: from discounting future gains to future losses. *Brain Res.* 1261, 65–74.
Yonelinas, A. P. (1994). Receiver–operating characteristics in recognition memory: evidence for a dual–process model. *J. Exp. Psychol. Learn. Mem. Cogn.* 20, 1341–1354.
Zarnhofer, S., Braunstein, V., Ebner, F., Koschutnig, K., Neuper, C., Reishofer, G., et al. (2012). The influence of verbalization on the pattern of cortical activation during mental arithmetic. *Behav. Brain Funct.* 8, 13.
Zhang, J. X., Feng, C. M., Fox, P. T., Gao, J. H., and Tan, L. H. (2004). Is left inferior frontal gyrus a general mechanism for selection? *Neuroimage* 23, 596–603.

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APPENDIX

EXAMPLES OF SENTENCES USED FOR TESTING REMEMBRANCE

Correct statements

1. The car of the woman is white.
2. He reads a Hebrew newspaper.
3. The couple buys for themselves a dog.
4. He calls the emergency service, when the cat jumps from the window.
5. She cries after the accident.
6. He gives vitamins to the cat.
7. He gives dog food to the cat.
8. He cleans the window with a cloth.
9. He was already once bitten by a dog.
10. He puts a dog bone on the grave.
11. Pictures hang above the TV set.
12. He reads the newspaper in the toilet.
13. She asserts that she drove slowly.
14. The curtains of the main character are checkered.
15. The cat is brown-beige.
16. He sleeps with the cat in bed.
17. In the kitchen there is a white water kettle.
18. The couple speaks about the professional carrier of the woman.
19. In the kitchen there is a pan on the oven.
20. In the kitchen there is a fan on the ceiling.

Incorrect statements

21. He has a roommate.
22. She wears a white top.
23. At the grave he kisses the woman.
24. She wears a skirt.
25. He reads a book.
26. She says that she drove too quickly.
27. He plays a videogame.
28. The bowl of the cat is red.
29. The couple sleeps with each other without the dog in bed.
30. The new dog's name is Bobby.
31. His friends eat Pizza in his apartment.
32. When he drives he wears no glasses.
33. The balloons from the room have different forms.
34. He offers the cat spaghetti at breakfast.
35. She puts a bunch of flowers on the grave.
36. The vacuum cleaner is blue.
37. In the kitchen hangs a chandelier.
38. He yells at the woman, when he sees her.
39. There are socks under the bed.
40. He makes phone calls in the toilet.

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A review of the neural and behavioral consequences for unitizing emotional and neutral information

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A special type of association, called a "unitization," is formed when pieces of information are encoded as a single representation in memory (e.g., "shirt" and "blue" are encoded as a "blue shirt"; Graf and Schacter, 1989) and typically are later reactivated in memory as a single unit, allowing access to the features of multiple related stimuli at once (Bader et al., 2010; Diana et al., 2011). This review examines the neural processes supporting memory for unitizations and how the emotional content of the material may influence unitization. Although associative binding is typically reliant on hippocampal processes and supported by recollection, the first part of this review will present evidence to suggest that when two items are unitized into a single representation, memory for those bound items may be accomplished on the basis of familiarity and without reliance on the hippocampus. The second part of this review discusses how emotion may affect the processes that give rise to unitizations. Emotional information typically receives a mnemonic benefit over neutral information, but the literature is mixed on whether the presence of emotional information impedes or enhances the associative binding of neutral information (reviewed by Mather, 2007). It has been suggested that the way the emotional and neutral details are related together may be critical to whether the neutral details are enhanced or impeded (Mather, 2007; Mather and Sutherland, 2011). We focus on whether emotional arousal aids or inhibits the creation of a unitized representation, presenting preliminary data, and future directions to test empirically the effects of forming and retrieving emotional and neutral unitizations.

Keywords: emotion, associative memory, unitization, integration, medial temporal lobes

A key feature of human memory is the ability not only to remember discrete pieces of information but also to form novel associations between those pieces of information. Whether we are trying to identify the acquaintances who work at the same company or the specific combination of physical characteristics that indicate that a particular plant is poisonous, we frequently draw on memory for associations. A special type of association, called a "unitization," can be formed when the pieces are encoded as a single representation in memory (e.g., the item "shirt" and the color "blue" are encoded as a "blue shirt"; Wollen et al., 1972; Graf and Schacter, 1989; Yonelinas, 2002; Diana et al., 2008, 2011). As Graf and Schacter (1989) describe, unitization can happen in one of two ways: either the items are perceived as having some underlying perceptual structure that leads them to be perceived as a single unit, or their co-occurrence implies a relationship that leads them to be combined together due to their presentation in space and time. Unitizations can be beneficial because they are typically reactivated in memory as a single unit, allowing access to the features of multiple related stimuli at once.

THE CREATION AND RETRIEVAL OF UNITIZATIONS

In this first section, we will review some of the neuroanatomy relevant to the formation and retrieval of unitized representations. We will also describe patient and neuroimaging data that can elucidate how unitizations are mnemonically encoded, and later accessed, in memory.

ANATOMICAL ORGANIZATION OF THE MEDIAL TEMPORAL LOBES, AND ITS RELATION TO UNITIZATION

Hippocampus and surrounding cortices

The medial temporal lobes have been described as having a functionally hierarchical structure (Lavenex and Amaral, 2000; Montaldi and Mayes, 2010), consisting of the parahippocampal cortex (PHC), perirhinal (PrC), and entorhinal (EC) cortices, and the hippocampus proper. It is still debated whether these regions comprise a single system which enables declarative memory (e.g., Squire and Zola-Morgan, 1991; Squire et al., 2007) or contribute differentially to the encoding and retrieval of individual items and the relationships between those items (e.g., Cohen and Eichenbaum, 1993; Aggleton and Brown, 1999; Diana et al., 2007; Staresina and Davachi, 2008). Although coverage of this debate is outside the purview of this review, understanding of the proposed hierarchy is critical to discerning how unitized representations may be encoded and subsequently retrieved (Staresina and Davachi, 2006, 2008).

Briefly, the PrC and PHC have reciprocal connections with both unimodal (e.g., auditory and visual association areas) and multimodal association areas (e.g., posterior and anterior association areas; Lavenex and Amaral, 2000). PrC and PHC are believed to be the first site of integration of information from all sensory cortices, and data have suggested that there is functional specialization even at this first stage, with PrC primarily receiving object information from visual cortex and TE/TEO and PHC primarily

receiving spatial information from the frontal and parietal cortices (Diana et al., 2007; Suzuki, 2010; also Bachevalier and Nemanic, 2008 for similar evidence from Rhesus macaques). As such, we can conceive of two possibilities for how the MTL may deal with unitized representations based on this differentiation. On the one hand, a to-be-unitized pair may be processed as a unitized object in regions within the dorsal or ventral visual processing stream (related to concepts of "object files" as originally conceived by Kahneman et al., 1992, and to the dual-system model of visual short-term memory proposed by Xu and Chun, 2006). This "pre-packaged" information could then be communicated to the PrC or PHC. On the other hand, the PrC may receive information about the separate to-be-unitized objects or object features and then begin the process of packaging them together – perceptually or mnemonically – into a single representation (e.g., Bussey et al., 2003; Bussey and Saksida, 2007; Kent and Brown, 2012) before passing on that information to the next regions in the hierarchy (see Cowell et al., 2010; Graham et al., 2010; Saksida and Bussey, 2010 for discussion of the role of the PRC in perception and memory for complex feature conjunctions).

Entorhinal cortex shares reciprocal connections with PrC and PHC, and it also receives direct inputs from multimodal association cortices. EC therefore receives input from all sensory modalities and is believed to play a greater role in the processing and integration of contextual information than of object information (Suzuki et al., 1997). EC does, however, receive object information from PrC and passes that information along to the hippocampus; most generally, the EC is considered to mediate much of the informational input to the hippocampus (Canto et al., 2008). Relative to other regions of MTL, less is known about the exact function of EC, but we can offer several possibilities. First, it is possible that because EC serves in this "gatekeeper" role of passing the hippocampus information from other brain regions (Hargreaves et al., 2005) – including PrC – that EC plays no direct role in the formation of unitizations. Instead, it may either pass pre-bound unitizations, formed in either the PrC or earlier regions of the ventral visual stream, to the hippocampus (if unitization happens before information reaches the hippocampus), or EC may pass information about individual objects or stimuli to the hippocampus, and unitization may take place within the hippocampus proper. Another alternative is that the EC itself is responsible for at least some processes relevant to forming unitizations, given its suggested role in contextual integration (Suzuki et al., 1997) and in subsequent correct recognition of verbal pairs (Jackson and Schacter, 2004). At present, these possibilities have not been distinguished, and so future research will be needed to explore the EC's role in memory for unitizations.

The hippocampus sits atop the anatomical hierarchy and receives well-integrated information from EC, PrC, and PHC (Mayes et al., 2007). The hippocampus projects this richly complex, integrated information back to cortical association areas, and this process – the feedback loop of information from cortical association areas, through MTL, and back to the cortex – is believed by some to be what produces the phenomenology of episodic memory (Squire, 1992). As we have alluded to, although it is clear that the hippocampus is essential for the formation of typical associations among stimuli (Aggleton and Brown, 1999; Eichenbaum et al., 2007), it is less clear whether the hippocampus is needed for the formation and retrieval of unitizations (Giovanello et al., 2006; Quamme et al., 2007). We will return to this debate in the next section of this review.

It is important to note that the interactions between these MTL regions may be complicated by the fact that these regions can have functional influences on one another without having direct anatomical connections (see also Damoiseaux and Greicius, 2009 for discussion). Lacy and Stark (2012) revealed that functional connectivity – the strength of correlation in activity among brain regions – was stronger among cortical regions of the MTL (PrC, EC, and PHC) than it was between these regions and the hippocampus. Conversely, hippocampal subfields had strong inter-field functional connectivity but little connectivity with the surrounding cortex. As such, it may not be sufficient to explore what each of these MTL regions contributes to unitized memory in isolation; rather, understanding the functional connections between these regions will likely be critical to understanding the genesis of unitized representations in the brain.

Amygdala

In reviewing how emotion may interact with the unitization process, we must also consider the role of the amygdala. The amygdala's role in the modulation of emotional memories – via its interaction with other MTL regions – has been well established (Gallagher and Chiba, 1996; Cahill and McGaugh, 1998; Kensinger and Schacter, 2006), and although its role has been investigated more thoroughly for memories that are fearful or aversive, it also plays a role in memories of pleasurable experiences (reviewed by LaBar, 2007). Animal research has demonstrated that the amygdala – particularly the lateral and basal nuclei – shares strong reciprocal connections with PrC, EC, and hippocampus, specifically in the subiculum and in subfield CA1 (Krettek and Price, 1977; Canteras and Swanson, 1992; Savander et al., 1997; Shi and Cassell, 1999; Pitkänen et al., 2000). Thus, there is substantial anatomical evidence indicating a reciprocal relationship between the amygdala and the anterior hippocampus as well as PrC. In addition, there is physiological and functional evidence of such a relationship. In rats, high frequency stimulation of the anterior hippocampus has been shown to produce long-term potentiation in the amygdala (Maren and Fanselow, 1985), and in patients, the amount of amygdala damage relates to the amount of hippocampal activity during an emotional memory task, and vice versa (Richardson et al., 2004). The amygdala also has robust connections to the visual cortex and regions along the ventral visual processing stream (Freese and Amaral, 2005; Duncan and Barrett, 2007). As such, there is an anatomical basis for predicting an interaction between the amygdala, PrC, and visual pathway, one that could influence the unitization process.

It has become clear that the amygdala does not act to enhance all aspects of a memory. Instead, the amygdala has selective effects on memory, enhancing some elements of a memory while having no beneficial impact – and sometimes even having an impairing effect – on other elements (reviewed by Kensinger, 2009; Mather and Sutherland, 2011). While not specifically discussing unitization, Mather (2007) described an "object-based framework" that is highly relevant to the process of unitization: when contextual

details (such as color, temporal order, etc.) are viewed as being integral or intrinsic to the emotional stimulus, emotional arousal (likely via activation of the amygdala; see Kensinger et al., 2011 for evidence) enhances the binding of those details. This finding suggests that amygdala engagement can enhance the process of unitization.

Having reviewed the anatomical hierarchy within the medial temporal lobes, we now move to examine the empirical evidence for how these structures help produce episodic memory for items, their associations, and unitized representations. We begin with a brief discussion of a common way that memory for items and their associations is tested in the laboratory: through assessments of recognition memory. We focus on a model that argues that recognition memory can be supported by dissociable processes – recollection (including memory for episodic details) and familiarity (roughly akin to item familiarity; Atkinson and Juola, 1974; Yonelinas, 2002) – that have in turn been argued to map on specifically to the hippocampus and PrC, respectively (Aggleton and Brown, 1999; Diana et al., 2007; Bowles et al., 2010). Understanding how these regions and processes interact to produce an episodic memory is critical to understanding how the brain may encode, store, and retrieve unitized representations and how emotion may impact those processes.

MEMORY THROUGH RECOGNITION

Often in the laboratory, memory for the relationship between two items is tested through recognition. In a typical paradigm, participants will study lists of unrelated paired associates (e.g., two semantically unrelated words, face-name pairs, etc.), and then memory for pairs or for individual items can be tested as part of an "old/new" recognition test. Although there are still some disagreements even among those who propose a dual-process model of recognition comprising recollection and familiarity (e.g., Yonelinas, 1994, 2002; Wixted, 2007), what is generally agreed upon is that recollection typically refers to the recall of specific episodic detail that was associated with the test stimulus: for example, a participant sees a recognition cue and retrieves specific knowledge unique to the context in which that cue was initially encountered, such as what information it appeared in conjunction with, what information temporally preceded or followed it, what thought was triggered by the information's presentation, and so on (Montaldi and Mayes, 2010). Familiarity, on the other hand, is assumed to require no such access to episodic details. It is characterized by the knowledge that a particular test stimulus has been encountered previously – sometimes referred to as a "feeling of knowing" (Montaldi and Mayes, 2010) – but is not accompanied by retrieval of other contextual or otherwise associated details. Although there are alternative accounts to this "dual-process" model of memory (e.g., Squire et al., 2007), our goal in this review is not to adjudicate between the models. Rather, our review will follow from a wealth of research broadly demonstrating behavioral and neural dissociations between these processes.

UNITIZATION IN THE BRAIN

A plethora of studies have supported a dual-process view not only of recognition memory but also of the MTL system (see Eichenbaum et al., 1994; Brown and Aggleton, 2001 for initial proposals). This research has revealed that the hippocampus is involved in associative binding of an item to its episodic context while the PrC plays a more dominant role in the representation of single items (see Diana et al., 2007; Eichenbaum et al., 2007 for reviews). An important caveat, however, and the one that we describe next, is that this hippocampal binding, and associated recollection, may not be necessary in cases of unitization.

Patient and imaging data support the notion that unitized representations can be supported by PrC and recognized via familiarity. To examine whether familiarity could contribute to the recognition of unitized representations, Diana et al. (2011) asked participants to view items presented on either a red or green background, and they were instructed either to imagine the item in the color of the background (the high-unitization condition), or to remember independently what color of background the item was paired with (low-unitization). Behaviorally, familiarity-based judgments were significantly higher in the high- vs. low-unitization condition, while recollection-based judgments did not differ. ERP data showed that the ERP correlates of familiarity – the early, fronto-central positivity – were significantly more apparent in the high- vs. low-unitization condition, while unitization demands had no effect on the ERP correlates for recollection. As noted by Diana and colleagues, their data – taken together with data from other studies that also revealed enhanced ERP correlates of familiarity on tasks encouraging unitization (e.g., Ecker et al., 2007; Diana et al., 2008; Bader et al., 2010) – provide relatively strong support for the proposal that unitization enhances familiarity-based recognition.

Although unitization may enhance the ability to recognize item associations on the basis of familiarity, Pilgrim et al. (2012) revealed that this may come at a cost when recognizing the individual items within the pair. They asked participants to study lists of single items, as well as pairs of words studied using either a unitization strategy (i.e., using mental imagery of the two items interacting in some way) or a non-unitization strategy (i.e., imagining the two items separately). Participants were then given a recognition test of single items from both the item-only and unitization/non-unitization conditions. At retrieval, the authors observed a reduced frontal effect, typically associated with familiarity-based retrieval, during recognition of items studied in the unitization condition relative to the item-only or non-unitization conditions. The authors interpret this result as suggesting that unitization limits familiarity-based access to items that have been combined into a unitized representation. Importantly, unitization did not affect overall item recognition accuracy: there was no difference in d', hit rate, or reaction time for items in those two conditions. Thus, unitization affected *how* the information was recognized (by familiarity or recollection) and not *whether* it was recognized. Although the authors describe this reduced familiarity signal as a potential "cost" of unitization, they note that it could alternatively be interpreted as a benefit of unitization: equivalent item recognition memory, in an equivalent amount of time, is produced without reliance on a familiarity signal. Regardless of the exact interpretation of these findings, the results of this study, along with those of Diana et al. (2008), suggest that the process of unitization may differentially affect the role of familiarity in recognizing the associations compared to the individual items, enhancing the

influence of familiarity on the former while reducing its influence on the latter.

Further evidence to suggest that unitization creates an associative representation that can be retrieved by processes typically associated with item memory or familiarity has come from two sets of data sampling patients with MTL amnesia. Giovanello et al. (2006) first showed, in a group of non-amnestic individuals, that recognition of unitized associations relies more on familiarity than recognition of non-unitized associations. They then discovered that patients with amnesia were better at differentiating between studied and rearranged pairs if the pairs formed compound words (e.g., correctly responding "old" to the studied words "blackmail" and "jailbird," but "new" to the rearranged word "blackbird") than if the pairs formed novel associations (e.g., "surgeon-arrow"). For non-amnestic controls, there was no such difference between the two types of associations. These data are consistent with the proposal that unitized representations can be remembered on the basis of item memory or familiarity, processes more likely to be spared in amnesia than those related to associative binding or recollection.

Quamme et al. (2007) presented similar findings: the researchers tested five amnesic patients, two of whom had undergone a left unilateral temporal lobectomy, damaging the hippocampus as well as PrC and EC, and three of whom were believed to have lesions restricted to the hippocampus as a result of cerebral hypoxia following cardiac arrest. When given pairs of unrelated nouns to study, hypoxic patients with intact rhinal cortices later recognized the pairs more readily if the words had been combined into a compound word with a novel definition (e.g., "cloud-lawn" would be defined as, "A yard used for sky-gazing.") than if the words were presented in a sentence (e.g., "The ___ could be seen from the ___"). The two patients with temporal lobectomies, exhibiting damage to the rhinal cortices, did not show any such benefit from unitization.

These data offer compelling evidence that the hippocampus is not necessary for the encoding and retrieval of unitized representations, and they further suggest a role for the rhinal cortices in the formation of unitizations. Further evidence for a role of the PrC in unitization has come from studies using functional MRI. Using a paradigm similar to that of Quamme et al. (2007), Haskins et al. (2008) directly tested the hypothesis that PrC can support the encoding of unitized representations. Healthy participants were given pairs of semantically unrelated nouns (e.g., "steam tree") and were asked to rate how well the words fit into a given sentence frame (no unitization), or they were given a novel definition for the compound of the two words and asked to rate how well they thought the definition fit the compound (unitization). They were then shown test pairs that were either intact from study or rearranged and had to indicate whether the words had been studied together or not. The imaging data, along with behavioral data from participants' ROCs, indicated that left PrC was more active during compound than sentence trials, and that its activity at encoding was predictive of correct familiarity-based recognition judgments at test.

Staresina and Davachi (2006) also offer functional MRI evidence that the PrC can support the encoding of unitized item-color information. In their task, participants viewed the verbal label of an item (e.g., "elephant") on a colored background, and were asked to imagine the item in the color of the background (e.g., for a red background, imagine a red elephant) and decide if the representation could plausibly appear in the real world or not. Participants were then given a surprise test in which they had to indicate if items were old or new, and if they judged an item to be old, they had to indicate with what color the item had been presented. While they observed that bilateral hippocampal activity at encoding predicted subsequent associative recognition success, encoding activity in left PrC was also found to be predictive of success at retrieving both the words and also the word-color pairs. They suggested that the PrC was able to support associative recognition for the item and its corresponding color because the color and item information had been unitized at encoding.

To directly test their hypothesis, in a second study, Staresina and Davachi (2008) used a similar encoding task, but they also asked the participants to make one of two semantic decisions about the item (judging its pleasantness or its plausibility). This manipulation allowed the researchers to assess how MTL subregions contribute to memory for those different types of detail. Consistent with their previous results, they found that encoding activity in the left hippocampus and bilateral PrC predicted subsequent associative recognition for item-color pairings. In contrast, only the hippocampus and not PrC predicted successful retrieval of the item-context (i.e., encoding task) association. If we consider the color to be associated via a process of unitization but the encoding task to be associated through other means, then these data offered further evidence that PrC may indeed help to encode unitized associations but not other forms of associative learning.

While these three functional MRI studies indicate that PrC offers an important contribution to the formation of associative memory through unitization, they still cannot elucidate the specific role that PrC might play in the unitization process. That is, it still remains unclear from these data whether PrC is responsible for assembling unitizations – actually concatenating together the different object features into a single unit – or if it may receive already-unitized representations from other regions and PrC encodes that pre-assembled representation. To test this, Staresina and Davachi (2010) conducted a third study systematically varying the unitization demands at encoding to investigate how PrC would track with increasing unitization requirement. The hypothesis was that if PrC activity showed a variable relation based on the varying unitization demand, it would suggest that the PrC plays a role in actually putting together novel unitizations. In their study, participants viewed objects that were intact, fragmented into two parts, or fragmented into four parts, and participants were asked to imagine the whole item in the color of the background and to determine its real-world plausibility. By including three fragmentation conditions, the researchers were able to vary how much the item needed to be unitized to succeed at the encoding task. Participants were given the same recognition task from Staresina and Davachi (2006), described above. As in Staresina and Davachi (2006), PrC activation at encoding – this time, bilaterally – was predictive of subsequent item and associative recognition success; however, PrC activation was unaffected by level of fragmentation. Rather, regions throughout the ventral visual stream tracked with increasing unitization demand. These data suggest that while PrC can support the mnemonic encoding of unitized associations, the

perceptual integration of a unitized representation may occur in earlier stages of processing.

The role of the PrC in unitization likely does not stop after encoding. Diana et al. (2010) asked participants to study nouns presented on a red or green background and to process the color either as an item feature – by imagining the item in that color – or as a contextual detail by imaging the item interacting with a stop sign (red) or dollar bill (green). Although control participants were able to retrieve the color information with equal probability, regardless of the encoding instructions, amnesic patients were more likely to retrieve the color information if it had been processed as an item feature rather than a contextual detail. fMRI results with healthy individuals revealed that PrC activity was associated with the retrieval of the color information if it had been studied as an item feature while PHC and hippocampal activity was associated with the retrieval of the color information if it had been studied as a contextual feature.

It is worth noting that domain in which information is presented and manipulated (e.g., whether the participant is creating a compound word or imagining the visual representation of an item) likely affects the neural processes that underlie successful unitization. Although to our knowledge, no study has directly contrasted the neural processes leading to integration by visual or verbal means, it seems plausible that tasks that require unitization of visual entities – such as those just described – would engage visual processing regions while tasks that achieve unitization through the creation of a new concept may engage semantic processing regions such as anterior temporal lobe (Lambon et al., 2010). Regardless of the domain in which the unitization occurs, however, one critical point remains true: it does not appear to be the case that hippocampal engagement is necessary for unitization to be successful.

The data reviewed in this section suggests three main conclusions: (1) Unitized associations can be remembered on the basis of familiarity and using processes typically associated with single item memory, but this effect of unitization may come at the cost of familiarity-based recognition of the individual components of the associated pair. (2) At an anatomical level, the data suggest that the hippocampus is not necessary for forming and encoding unitizations. Instead, PrC may play a role in the mnemonic encoding and retrieval of those unitizations, although (3) at encoding, PrC may, instead or in addition, receive already-unitized information from other brain regions and then work to store that unitized representation into long-term memory. In the section below, we outline the predictions that each of these findings makes with regard to the effect of emotion on memory for unitized representations.

EMOTION AND UNITIZATION

It has been well established that emotional information is handled differently in memory from non-emotional information, with emotional information typically receiving a mnemonic benefit (reviewed by Hamann, 2001; Kensinger, 2009). The emotionality of an experience is often characterized along two orthogonal dimensions: arousal (how exciting or calming an experience is) and valence (how pleasant or unpleasant; Russell, 1980). Because the bulk of research examining the effect of emotion on memory has focused on the dimension of arousal (Cahill et al., 1994; Cahill and McGaugh, 1995), and because arousal is thought to be the main factor that influences amygdala activity (Adolphs et al., 2001; Sharot and Phelps, 2004; Berntson et al., 2007), we will focus our review on the contributions of emotional arousal to emotional memory. It is important to note, however, that valence can influence associative memory as well (Pierce and Kensinger, 2011) and may interact with arousal to influence both the subjective qualities of a memory (Talarico and Rubin, 2003; Sharot and Phelps, 2004; Zimmerman and Kelley, 2010) and also the way that the amygdala interacts with visual and prefrontal processes (e.g., enhanced connectivity between amygdala and middle occipital gyrus and amygdala and inferior frontal gyrus during encoding of high-arousal negative items and low-arousal positive items; Mickley Steinmetz et al., 2010).

To date, there has been little research that specifically has examined the effect of arousal on unitization. There have, however, been many studies that have more generally assessed the effect of arousal on recollection and familiarity, and on the associative binding of item features and contextual details. In the sections below, we review the research on the effects of arousal on memory that we believe can lead to informed predictions regarding the effects of arousal on unitization.

THE EFFECTS OF AROUSAL ON ASSOCIATIVE BINDING: IMPLICATIONS FOR UNITIZATION

Although the effects of arousal on associative binding initially seemed inconsistent – with arousal sometimes enhancing the binding of details (e.g., MacKay et al., 2004) and at other times having no effect, or impairing, such binding (e.g., Kensinger and Schacter, 2006; Bergmann et al., 2012; note that the latter examines interactions between both valence and arousal) – more recent accounts have proposed a unified framework for understanding the complex pattern. Mather (2007) proposed an "object-based" framework, with arousal enhancing the binding of information encoded as an item feature but not of information encoded as a contextual detail (see also Kensinger, 2007, 2009). This framework can account for much of the extant data, but there are some exceptions, when arousal does not enhance memory for intra-item features (Guillet and Arndt, 2009) and when it does enhance memory for inter-item binding (Pierce and Kensinger, 2011).

Recognizing the need to account for these contradictory patterns, Mather and Sutherland (2011) proposed the "Arousal-Biased Competition" (ABC) model, describing how arousal may bias resources toward the most conspicuous or goal-relevant stimuli. Thus, if a single item (e.g., a snake) gains priority, then arousal will enhance the binding of the features of that item (e.g., its color, form). But if the pairing of items takes on importance (e.g., the snake and its owner) then arousal will enhance the binding of that association. In other words, it is not the *type* of detail (item vs. contextual or intra- vs. inter-item associations) that predicts the effect of arousal but the *goal relevance* of the detail (see related discussion by Levine and Edelstein, 2009). Although it is always the case that goal-relevant information will be prioritized, according to ABC, arousal exaggerates this prioritization; thus, arousal will enhance the binding of goal-relevant features and will impair the binding of features that are not goal relevant.

In this context, the effect of arousal on associative binding will depend critically on the way the to-be-bound pieces of information are initially processed or perceived. On the one hand, because unitization requires that pieces of information be processed as a coherent whole, all features that are being bound into a unitized representation may be goal relevant. If true, then arousal may lead to a beneficial effect on the process of unitization. On the other hand, because arousing features can capture attention and become prioritized for processing, the presence of those arousing features may make it harder to attend to the other features present at the same time, thereby making the creation of a unitization harder to achieve. Each of these possibilities will be expanded upon in the next sections.

WHY AROUSAL MAY ENHANCE UNITIZATION

As described earlier, neuroimaging data (e.g., Staresina and Davachi, 2010) suggest that visual regions such as those within the ventral visual pathway can be responsible for the initial formation of unitized representations. Thus, unitizations may be created before the information reaches the MTL system. Separate literatures have revealed that activity in these visual regions can be modulated by the arousing content of information. Neuroimaging studies have shown that participants tend to exhibit greater activity in visual cortex and ventral visual stream when viewing emotional vs. non-emotional images (Vuilleumier et al., 2001, 2004; Compton, 2003; Mather et al., 2006), likely because of modulation of visual processing by the amygdala. These data suggest that processing of emotional items within the visual cortex may be prioritized, leading these items to be attended to before neutral items (Öhman and Mineka, 2001; Öhman et al., 2001), to hold attention longer (LaBar et al., 2000; Nummenmaa et al., 2006; Knight et al., 2007), and to be associated with greater encoding activity in visual regions than non-emotional items (Bradley et al., 2003; Mather et al., 2006).

Putting these literatures together: if visual regions such as those along the ventral visual pathway are responsible for the initial formation of unitized representations, the presence of arousal could facilitate activation within those regions, enabling the rapid creation of a unitization. In addition, these literatures may suggest that unitizations containing an arousing component would require less cognitive effort to create than unitizations that contain only neutral information. Because arousing information benefits from prioritized processing, it may be more rapidly and easily integrated unitized. On the other hand, neutral information – which is not privy to such prioritization – may require more cognitive effort to successfully unitize.

Several investigations have demonstrated that when non-emotional information is encoded as a feature of an emotional item, memory for the relationship between the emotional and non-emotional information is enhanced. For example, two recent studies (Mather and Nesmith, 2008; Nashiro and Mather, 2010) demonstrated that when participants passively viewed non-emotional and emotionally arousing pictures at different locations on a computer screen, their memory for the location of emotionally arousing pictures was significantly better than their memory for the location of non-emotional pictures. Mather and Nesmith (2008), in particular, offer evidence for the above points about emotional information being integrated with relatively little cognitive effort: In Experiment 4 of that investigation, the authors varied the amount of time participants had to view pictures (relative to the amount of study time provided in the first three experiments) to determine if location memory tracked with the amount of time participants had to view pictures. The authors found that memory for the location of pictures was independent of how long the pictures were presented. Moreover, it was shown that picture-location conjunction memory for non-emotional pictures was not impaired when those pictures were presented at the same time as emotional pictures, even when encoding time was limited. From this evidence, the authors conclude that arousing pictures did not capture attention for any extended period of time (or else picture-location memory for concurrent non-emotional pictures would be impaired), suggesting that picture-location binding for arousing pictures must happen quickly and with relatively little effort.

Another recent behavioral study (Guillet and Arndt, 2009) demonstrated that inter-item memory could be enhanced by arousal, as well. Mnemonic binding of verbal pairs was enhanced if one of the target words was arousing (i.e., a "taboo" word). Memory for the association between the taboo word and a neutral word was enhanced relative to when the neutral word was paired with another neutral word, or paired with a negative non-arousing word. Though these data offer evidence that arousal may enhance the formation of inter-item associations, it is important to note that relatively little is known about what makes taboo words – and their associations – memorable. Madan et al. (2012), for example, demonstrated that arousal is only one dimension that separates taboo words from other emotional high-arousal and emotional low-arousal words. Those authors used multidimensional scaling for several dimensions of normed ratings (e.g., "familiarity," "offensiveness," "imageability") of neutral, emotional, and taboo words to show that arousal alone does not clearly differentiate taboo words from other emotional words; rather, some undetermined combination of other stimulus characteristics is likely to better differentiate those stimuli. Therefore, it is unclear whether it is the arousing nature of taboo words that leads them to be better associated in Guillet and Arndt (2009), or if some other set of characteristics – like offensiveness or "tabooness" that may be separate from arousal – is driving those effects. Moreover, Madan et al. (2012) demonstrate that across a number of pair types – with pairs containing only taboo, only moderately arousing negative, only neutral, or any combination thereof – the presence of emotional arousal only ever improved item memory, and never improved association memory.

WHY AROUSAL MAY IMPAIR UNITIZATION

The prior discussion of goal relevance highlights an important caveat regarding the beneficial effect of arousal on unitization: Participants would need to find all of the to-be-unitized components to be goal relevant in order for arousal to facilitate their unitization. This goal relevance would likely be achieved in a task that directed participants to integrate the various features, as the task instructions would make both items relevant. But if integration is not emphasized, arousal may instead impair the unitization by focusing perceptual and cognitive resources only on the arousing feature, thereby preventing unitization with the other features.

If attention is directed to the arousing information and not distributed to all elements of the to-be-unitized set, the unitization may fail.

Arousing information can capture visual attention and can be processed in a prioritized fashion. Studies that record participants' eye gaze patterns while they view either arrays of emotional and non-emotional stimuli or complex visual scenes have shown that participants initially saccade to emotional information more quickly, and they saccade more frequently to the emotional information than to neutral information (LaBar et al., 2000; Öhman and Mineka, 2001; Öhman et al., 2001; Mather and Knight, 2006; Knight et al., 2007). In studies that require participants to detect two or more target items in a rapidly presented stream of stimulus items, a phenomenon known as the "attentional blink" is typically observed: participants readily detect the first target item in the rapid stream, but often miss the subsequent target item (e.g., Chun and Potter, 1995). The presumption is that attentional resources are directed toward detecting the first target item, resulting in the second item being missed. However, when the second target item is emotionally arousing, the attentional blink effect is attenuated. Despite presumably depleted attentional resources, participants can still detect the emotional second target item (Anderson and Phelps, 2001; Keil and Ihssen, 2004; Anderson, 2005). These findings suggest that when attentional resources are limited, emotionally arousing items are preferentially processed over neutral items.

This prioritized processing of the arousing information can result in poor processing of temporally- or spatially-proximate information (e.g., Easterbrook, 1959). These factors can combine to create instances in which the arousing elements of an event (e.g., a smashed car) are remembered at the expense of the surrounding, non-emotional details (e.g., details of the street on which the accident occurred; see reviews by Buchanan and Adolphs, 2002; Reisberg and Heuer, 2004; Levine and Edelstein, 2009). Indeed, in laboratory studies using complex visual scenes as encoding stimuli, a "trade-off" in memory is often observed: participants exhibit better memory for emotional than non-emotional items that appeared in the scenes, and their memory for the background details is better when those backgrounds are presented with neutral rather than emotional items (e.g., Kensinger et al., 2005). Neurally this trade-off is associated with increased activity in the middle temporal gyrus, among other regions (Waring and Kensinger, 2011). This region within the ventral visual stream is more active during the encoding of scenes for which the emotional item is subsequently remembered and the background forgotten than for scenes in which both the item and background are remembered, suggesting that visual resources may be preferentially processing the emotional information at the expense of the non-emotional information.

These findings may relate to the process of unitization for an emotional and a non-emotional feature. If sensory-processing regions preferentially process the emotional features over the non-emotional feature, the success of the unitization could be compromised. By giving preference to the emotional information, the unitization may not equitably represent both the emotional and non-emotional components. Instead, the unitization may be dominated by the emotional information, or the unitization may fail altogether because processing resources are focused on the emotional information to the exclusion of the non-emotional details.

Further evidence that emotion may impair the formation of unitizations – particularly in the case of negative emotional information – comes from a study by Okada et al. (2011). In that study, participants were asked to learn novel pairs consisting of neutral faces paired with positive, negative, or neutral words while undergoing an fMRI scan. The researchers found a strong negative correlation between left amygdala activity during the encoding of negative pairs and subsequent memory performance, suggesting that amygdala activation at encoding may disrupt the formation of negative associations. It is important to note, though, that the opposite effect was observed for positive face-name pairs: increases in amygdala activation were related to better subsequent memory for those pairs, suggesting that the effect of arousal may depend on the valence of the information to be remembered.

THE MNEMONIC INFLUENCES OF AROUSAL: IMPLICATIONS FOR UNITIZATION

One of the most-often replicated effects of arousal on memory is the creation of a subjectively vivid memory (Phelps and Sharot, 2008; Sharot and Yonelinas, 2008; Zimmerman and Kelley, 2010). The beneficial effects of arousal on memory are often detected on tasks that assess not only recognition rates but also the subjective qualities of a memory. For instance, even when recognition rates do not differ between arousing and neutral stimuli, participants are often still more likely to say that they vividly recollect emotional items (Ochsner, 2000; Talarico and Rubin, 2003; Sharot et al., 2004). Although this effect may sometimes reflect a biased endorsement of emotional memories (Windmann et al., 2002; Dougal and Rotello, 2007), sometimes it seems to correspond with an improved ability to remember at least some features of an arousing item's presentation (Neisser and Harsch, 1992; Kensinger and Corkin, 2003; see review by Mather, 2007). By contrast, arousal often does not enhance the familiarity of items, and when it does, it often seems to do so for both studied and non-studied items alike, increasing both correct and incorrect endorsements and having little effect on memory discriminability (e.g., Sharot et al., 2004).

Consider that one of the predominant reasons why there is a mnemonic benefit for unitizations may be because of their ability to be recognized on the basis of familiarity (Diana et al., 2008, 2011; but see Mickes et al., 2010). If so, then the literature just reviewed may suggest that the relative benefit of unitization would be less for emotional associations than for neutral associations. That is, arousal may enhance processes that are connected to the recollection of information more than those connected to the familiarity of information, while unitizations may do the opposite.

At a neural level, it is less clear whether there is a distinction between the memory regions most influenced by arousal and those implicated in unitization. Certainly, much emphasis has been placed on the ability for arousal to modulate *hippocampal* function, via connections between the amygdala and the hippocampus. The initial studies examining the effect of arousal on memory consolidation focused on interactions between the amygdala and hippocampus proper (reviewed by McGaugh, 2004) and subsequent neuroimaging studies in humans have followed suit

(reviewed by Phelps, 2004), often focusing on the correlations or co-activations between the amygdala and the hippocampus during the formation or retrieval of an emotional memory (e.g., Dolcos et al., 2004; Kensinger and Corkin, 2004). Yet the amygdala also shares strong reciprocal connections with the PrC (Pitkänen et al., 2000; Kajiwara et al., 2003). A recent study revealed that stimulation of the amygdala could lead to induction of synaptic plasticity (i.e., long-term potentiation) within the PrC (Perugini et al., 2012), demonstrating a functional connection between the two regions. Thus, the finding that unitizations rely less on the hippocampus and more on the PrC makes no strong prediction with regard to the effect of emotion on unitization. The reciprocal connections between the amygdala and the PrC appear to be sufficiently strong to enable arousal-driven modulation, though of course it remains an open question whether such modulation would occur during the encoding or retrieval of unitizations.

As noted earlier, if unitizations rely on processes within the ventral visual processing stream, the amygdala activation that occurs during the experience of arousal would be likely to modulate processing within that stream (Anderson, 2005; Vuilleumier, 2005). There is ample evidence that the amygdala sends strong back-projections to regions through the sensory cortices (Amaral and Price, 1984; Iwai and Yukie, 1987; Morris et al., 1998), and this prioritized processing may facilitate the creation of a unitization. Thus, arousal could enhance the process of unitization either through modulation of medial temporal-lobe processes or through modulation of earlier sensory processes.

THE EFFECTS OF AROUSAL ON UNITIZATION: PRELIMINARY EVIDENCE

We Murray and Kensinger (2012) conducted a study to examine the effect of arousal on associative binding when unitization is encouraged. We asked participants to study pairs of words and to either maintain separate mental images of the items (non-integrated) or to create an integrated, interactive mental image of the two items (integrated), a task similar to that described in Pilgrim et al. (2012). Some pairs contained an emotional and a neutral word, and other pairs contained two neutral words. Each study pair was displayed for 2, 4, or 6 s, and after each pair participants were asked to report the vividness of the two individual images (non-integrated) or one unified image (integrated) they were able to generate.

Participants consistently rated their imagery success as being high for emotional pairs, regardless of the length of the encoding trial, but they reported little success in generating images for neutral pairs during short (2-s) encoding trials. These results are consistent with the prediction that arousal would facilitate the process of unitization: When arousal was present, participants were able to create an image that integrated two distinct items, even with little time to do so.

Participants were then given a surprise cued recall test in which they were given a single studied word and asked to provide its paired counterpart. Because this was an associative task, we unsurprisingly found that pairs studied in the integration condition were better recalled than those studied in the non-integration condition. Conversely, on an item recognition test, performance was better in the non-integrated condition than in the integrated one. This finding is generally consistent with evidence presented earlier, suggesting that although the formation of unitizations can enhance memory for associations, this unitization sometimes comes at the cost of gaining access to the individual item representations (Pilgrim et al., 2012).

The twist, however, was that the integration benefit was disproportionately *greater* for neutral pairs than for pairs containing an emotion word. Although participants had an easier time generating the integrated images for the emotional pairs, they showed *less* of a mnemonic benefit from integration of those pairs. At the broadest level, these data suggest that *forming* unitizations – actually assembling together the different perceptual and semantic features – and *remembering* those unitizations in long-term memory could be differentially affected by arousal. It is interesting to note that this distinction parallels one noted by Zimmerman and Kelley (2010); they reported that participants gave higher judgments-of-learning to emotional pairs than to neutral ones but actually remembered the emotional pairs less well. When reviewing this study, Madan et al. (2012) suggested that the participants may have applied less effort when forming associations of those emotional items, an explanation that is also consistent with our data. It may be the case that if information is more easily unitized – perhaps via processes implemented in visual processing regions – the mnemonic storage of that unitization is less effortful and therefore less durable.

FUTURE DIRECTIONS AND CONCLUSION

FUTURE DIRECTIONS

The research we have reviewed suggests the importance of distinguishing the effects of arousal on the initial process of forming unitizations from the process of storing those unitizations over the long term. Future research would do well to examine whether – if these processes were distinguished, perhaps using methods similar to Staresina and Davachi (2010) – arousal would have different effects on these two general types of processes.

It is also possible that the presence of arousal may lead to a shift from conceptual to perceptual binding processes in creating unitizations (see Graf and Schacter, 1989 for discussion of the contribution of these different processes). In discussing the neural architecture that may underlie encoding of emotional and non-emotional unitization, we have offered that emotional unitizations may be supported by interactions between the amygdala, ventral visual stream, and PrC, suggesting that such unitizations may rely on more perceptual linkages (e.g., what a poisonous plant looks like). Non-emotional unitizations, by contrast, may more often be supported by conceptual processes, perhaps requiring stimulus elaboration to effectively concatenate (e.g., realizing that the blanket, watermelon, and basket go together as a picnic). Although further empirical testing of this hypothesis is required, a first set of neuroimaging data (Murray and Kensinger, 2013) is consistent with this hypothesis, with successful integration of emotional pairs resulting in disproportionate activation within visual regions and successful integration of neutral pairs resulting in greater activation within prefrontal regions. Moreover, amygdala activity during negative integration was negatively correlated with activity in prefrontal and MTL regions, suggesting that amygdala engagement may disrupt prefrontal and MTL processes, consistent with the finding of Okada et al. (2011).

Emotional arousal, then, may shift unitization processes away from more conceptual ones implemented by prefrontal engagement and toward more perceptual ones implemented within visual regions. These different types of processes (perceptual vs. conceptual) may have differential downstream effects on subsequent memory for the unitizations. Conceptual elaboration may be a slower, more laborious process, but it may lead to a more deeply encoded, and more durable, representation. By contrast, perceptual integrations may happen rapidly, but be less durable over time. In other words, there may be a levels-of-processing effect (Craik and Lockhart, 1972), leading to a stronger and more durable memory trace for unitizations formed using prefrontal and MTL processes than for unitizations formed with disproportionate use of visual processes.

It would be informative for future research to examine how arousal affects the durability of unitizations. On the one hand, if the main effect of arousal relates to the way in which unitizations are initially formed, and if the processes creating unitizations for arousing items are less effortful and less "deep," then it might be expected that the decay rate for emotional unitizations would be faster than for neutral unitizations. On the other hand, however, the consolidation hypothesis (Müller and Pilzecker, 1900), suggests that after information is initially encoded it remains in a fragile state before being solidified into memory (see review by McGaugh, 2000). The consolidation process is relatively slow, and one proposed reason is to give any associated emotional response sufficient time to influence the consolidation process (McGaugh, 2000; Phelps, 2004). Indeed, there is robust evidence that arousal often enhances the consolidation of information, such that the beneficial effects of arousal are more likely to be apparent after longer delays than after shorter ones. This pattern of results has been shown not only in assessments of item memory (Sharot and Phelps, 2004) but also in tests of associative memory (Pierce and Kensinger, 2011; however, see Szpunar et al., 2012 for evidence that memory for details of imagined future autobiographical events is better for positive and negative than neutral events after a 10-min delay, but better for positive and *neutral* than negative events after a 24-h delay). Thus, it is possible that even if emotional unitizations are less "deep" and are maintained less well over relatively short delays (e.g., 30 min), they may have a shallower forgetting curve than neutral unitizations, making them more durable over longer delays. Adjudicating between these alternatives – by assessing memory for unitizations after multiple delays, or by disrupting consolidation through a retroactive interference task – would appear to be important for determining whether arousal primarily exerts its effects on unitization through processes that occur as the unitization is initially formed or whether the effects continue as that unitization is stored.

As we have noted earlier, the neural processes that underlie the formation and retrieval of unitizations are likely to depend in some way on the verbal or visual demands of the unitization. Although verbal unitizations (e.g., novel compound words; Giovanello et al., 2006; Quamme et al., 2007; Haskins et al., 2008) and visual unitizations (e.g., assembling a fragmented item and imagining it in a specified color; Staresina and Davachi, 2010) share some similarity – that is, they can be performed without reliance on hippocampal processing – no study has directly contrasted the neural correlates supporting their creation or retrieval. Emotion may also affect the unitization process differently, depending on the modality of processing. The amygdala can influence both visual processing (Vuilleumier et al., 2001, 2004; Compton, 2003; Mather et al., 2006) and semantic processing (Skipper et al., 2011), but the extent to which those influences differ for visual and verbal unitization – or on tasks that require some combination thereof (e.g., Staresina and Davachi, 2006, 2008; Murray and Kensinger, 2012) – is currently unknown. Therefore, we believe a fruitful future investigation would employ both verbal and visual unitization of emotional and non-emotional information, in an attempt to elucidate the similarities and differences between those two domains.

One area that we have not discussed to this point is how unitization processes may be utilized in the creation of autobiographical memories. Current theories of autobiographical retrieval suggest that it is a reconstructive process (see reviews by Conway, 1996; Holland and Kensinger, 2010) in which memories of our past are reconstructed at retrieval from our stores of autobiographical knowledge. This reconstructive nature imparts flexibility on retrieval from events in our past: the same event may be described differently at different time points. Autobiographical details also can be intentionally recombined into past events that did not occur, or into simulated, plausible future events. In one fMRI study, Addis et al. (2009) asked participants to report details of autobiographical events (i.e., the "who," "what," and "where") during a pre-scan session, and then directed those participants to imagine novel past and future events that consisted of recombined details from participants' actual memories. For example, if the participant reported memories of "Jess buying a lottery ticket at a convenience store," "Eating chicken fajitas with Cathy at Border's Café," and "Buying a flat screen TV with John at Best Buy" the participant may be asked to imagine a novel past or future event that involved "John," "Border's Café," and "lottery ticket." One could conceive of this process as being similar to unitization in that participants must take previously unrelated details and combine them into a single representation. A key difference however, is that in these tasks participants are asked to generate a representation of a new *event*, localized in time and space. To our knowledge, no tasks of unitization require this type of temporal or spatial localization of the representation. Perhaps because of this key difference, in the studies by Addis et al. (2009), this imaginative generation was shown to recruit activity in bilateral hippocampus, as well as activity in anterior prefrontal cortex and angular gyrus. These results suggest that whereas unitization of two words or items into a new representation may be accomplished in the absence of hippocampal processing (e.g., Giovanello et al., 2006; Staresina and Davachi, 2010), when new representations are created as *events* anchored in time and space, this may require the hippocampus.

CONCLUSIONS

The literature reviewed here suggests that unitized associations can be formed and retrieved using dissociable processes from those used to support memory for other associative memories. Unitized associations can be remembered on the basis of familiarity and in the absence of hippocampal function. Their formation

appears to be supported by some combination of processing within sensory-processing regions and within the rhinal cortex, although additional research is needed to further specify the involvement of these regions.

At least within a laboratory setting, when unitization is the specified goal, arousal appears to enhance the ability to form an integrated representation; this representation can be formed with high success even when under time pressure. Yet arousal does not enhance the ability to remember that unitized representation over the long-term, revealing a distinction between facilitated *formation* of a unitization and facilitated *retention* of that unitization. Further research will be needed to elucidate the reasons for these distinctions, but we suggest that arousal may facilitate the formation of unitizations via perceptual processing, whereas unitization for neutral items may be more likely to recruit conceptual processes implemented within prefrontal and MTL regions.

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REFERENCES

Addis, D. R., Pan, L., Vu, M. A., Laiser, N., and Schacter, D. L. (2009). Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imaging and remembering. *Neuropsychologia* 47, 2222–2238.

Adolphs, R., Denburg, N. L., and Tranel, D. (2001). The amygdala's role in long-term declarative memory for gist and detail. *Behav. Neurosci.* 115, 983–992.

Aggleton, J. P., and Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav. Brain Sci.* 3, 425–444.

Amaral, D. G., and Price, J. L. (1984). Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J. Comp. Neurol.* 230, 465–496.

Anderson, A. K. (2005). Affective influences on the attentional dynamics supporting awareness. *J. Exp. Psychol. Gen.* 134, 258–281.

Anderson, A. K., and Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 411, 305–309.

Atkinson, R. C., and Juola, J. F. (1974). "Search and decision processes in recognition memory," in *Contemporary Developments in Mathematical Psychology: Vol. 1. Learning, Memory & Thinking*, eds D. H. Krantz, R. C. Atkinson, R. D. Luce, and P. Suppes (San Francisco: Freeman Press), 243–293.

Bachevalier, J., and Nemanic, S. (2008). Spatial memory in monkeys as measured with the visual paired-comparison task: effects of selective hippocampal, perirhinal and areas TH/TF lesions. *Hippocampus* 18, 64–80.

Bader, R., Mecklinger, A., Hoppstädter, M., and Meyer, P. (2010). Recognition memory for one-trial-unitized word pairs: evidence from event-related potentials. *Neuroimage* 50, 772–781.

Bergmann, H. C., Rijpkema, M., Fernández, G., and Kessels, R. P. C. (2012). The effects of valence and arousal on associative working memory and long-term memory. *PLoS ONE* 7:e52616. doi:10.1371/journal.pone.0052616

Berntson, G. G., Bechara, A., Damasio, H., Tranel, D., and Cacioppo, J. T. (2007). Amygdala contribution to selective dimensions of emotion. *Soc. Cogn. Affect. Neurosci.* 2, 123–129.

Bowles, B., Crupi, C., Pigott, S., Parrent, A., Wiebe, S., Janzen, L., et al. (2010). Double dissociation of selective recollection and familiarity impairments following two different surgical treatments for temporal-lobe epilepsy. *Neuropsychologia* 48, 2640–2647.

Bradley, M. M., Sabatinelli, D., Lang, P. J., Fitzsimmons, J. R., King, W., and Desal, P. (2003). Activation of the visual cortex in motivated attention. *Behav. Neurosci.* 117, 369–380.

Brown, C. M., and Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61.

Buchanan, T. W., and Adolphs, R. (2002). "The role of the human amygdala in emotional modulation of long-term declarative memory," in *Emotional Cognition: From Brain to Behavior*, eds S. Moore and M. Oaksford (Amsterdam: John Benjamins Publishing), 9–34.

Bussey, T. J., and Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus* 17, 898–908.

Bussey, T. J., Saksida, L. M., and Murray, E. A. (2003). Impairments in visual discrimination after perirhinal cortex lesions: testing "declarative" vs. "perceptual-mnemonic" views of perirhinal cortex function. *Eur. J. Neurosci.* 17, 649–660.

Cahill, L., and McGaugh, J. L. (1995). A novel demonstration of enhanced memory associated with emotional arousal. *Conscious. Cogn.* 4, 410–421.

Cahill, L., and McGaugh, J. L. (1998). "Modulation of memory storage," in *Findings and Current Opinion in Cognitive Neuroscience*, eds L. R. Squire and S. M. Kosslyn (Cambridge: MIT Press), 85–90.

Cahill, L., Prins, B., Weber, M., and McGaugh, J. L. (1994). Adrenergic activation and memory for emotional events. *Nature* 371, 702–704.

Canteras, N. S., and Swanson, L. W. (1992). Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J. Comp. Neurol.* 8, 180–194.

Canto, C. B., Wouterlood, F. G., and Witter, M. P. (2008). What does the anatomical organization of the entorhinal cortex tell us?. *Neural Plast.* 2008, 1–18. doi:10.1155/2008/381243

Chun, M. M., and Potter, M. C. (1995). A two-stage model for multiple target detection in rapid serial visual presentation. *J. Exp. Psychol. Hum. Percept. Perform.* 21, 109–127.

Cohen, N. J., and Eichenbaum, H. (1993). *Memory, Amnesia, and the Hippocampal System*. Cambridge, MA: MIT Press.

Compton, R. J. (2003). The interface between emotion and attention: a review of evidence from psychology and neuroscience. *Behav. Cogn. Neurosci. Rev.* 2, 115–129.

Conway, M. A. (1996). "Autobiographical knowledge and autobiographical memories," in *Remembering Our Past: Studies in Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 67–93.

Cowell, R. A., Bussey, T. J., and Saksida, L. M. (2010). Components of recognition memory: dissociable cognitive processes or just differences in representational complexity? *Hippocampus* 20, 1245–1262.

Craik, F., and Lockhart, R. S. (1972). Levels of processing: a framework for memory research. *J. Verbal Learn. Verbal Behav.* 11, 671–684.

Damoiseaux, J. S., and Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Struct. Funct.* 213, 525–533.

Diana, R. A., Van den Boom, W., Yonelinas, A. P., and Ranganath, C. (2011). ERP correlates of source memory: unitized source information increases familiarity-based retrieval. *Brain Res.* 1367, 278–286.

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn. Sci. (Regul. Ed.)* 12, 379–386.

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2008). The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. *J. Exp. Psychol. Learn. Mem. Cogn.* 34, 730–740.

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2010). Medial temporal lobe activity during source retrieval reflects information type, not memory strength. *J. Cogn. Neurosci.* 22, 1808–1818.

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 42, 855–863.

Dougal, S., and Rotello, C. M. (2007). "Remembering" emotional words is based on response bias, not recollection. *Psychon. Bull. Rev.* 66, 183–201.

Duncan, S., and Barrett, L. F. (2007). The role of the amygdala in visual awareness. *Trends Cogn. Sci. (Regul. Ed.)* 11, 190–192.

Easterbrook, J. A. (1959). The effect of emotion on cue utilization and the organization of behavior. *Psychol. Rev.* 66, 183–201.

Ecker, U. K. H., Zimmer, H. D., and Groh-Bordin, C. (2007). Color and context: an ERP study on intrinsic and extrinsic feature binding in episodic memory. *Mem. Cognit.* 35, 1483–1501.

Eichenbaum, H., Otto, T., and Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behav. Brain Sci.* 17, 449–517.

Eichenbaum, H., Yonelinas, A. P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152.

Freese, J. L., and Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J. Comp. Neurol.* 486, 295–317.

Gallagher, M., and Chiba, A. A. (1996). The amygdala and emotion. *Curr. Opin. Neurobiol.* 6, 221–227.

Giovanello, K. S., Keane, M. M., and Verfaellie, M. (2006). The contribution of familiarity to associative memory in amnesia. *Neuropsychologia* 44, 1859–1865.

Graf, P., and Schacter, D. L. (1989). Unitization and grouping mediate dissociations in memory for new associations. *J. Exp. Psychol.* 15, 930–940.

Graham, K. S., Barense, M. D., and Lee, A. C. (2010). Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia* 48, 831–853.

Guillet, R., and Arndt, J. (2009). Taboo words: the effect of emotion on memory for peripheral information. *Mem. Cognit.* 37, 866–879.

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends Cogn. Sci. (Regul. Ed.)* 5, 394–400.

Hargreaves, E. L., Rao, G., Lee, I., and Knierim, J. J. (2005). Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. *Science* 308, 1792–1794.

Haskins, A. L., Yonelinas, A. P., Quamme, J. R., and Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron* 59, 554–560.

Holland, A. C., and Kensinger, E. A. (2010). Emotion and autobiographical memory. *Phys. Life Rev.* 7, 88–131.

Iwai, E., and Yukie, M. (1987). Amygdalofugal and amygdalopetal connections with modality-specific visual cortical areas in macaques *(Macaca fuscata, M. mulatta,* and *M. fascicularis*). *J. Comp. Neurol.* 261, 362–387.

Jackson, O. III, and Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage* 21, 456–462.

Kahneman, D., Treisman, A., and Gibbs, B. J. (1992). The reviewing of object files: object-specific integration of information. *Cogn. Psychol.* 24, 175–219.

Kajiwara, R., Takashima, I., Mimura, Y., and Iijima, T. (2003). Amygdala input promotes spread of excitatory neural activity from perirhinal cortex to the entorhinal-hippocampal circuit. *J. Neurophysiol.* 89, 2176–2184.

Keil, A., and Ihssen, N. (2004). Identification facilitation for emotionally arousing verbs during the attentional blink. *Emotion* 4, 23–35.

Kensinger, E. A. (2007). Negative emotion enhances memory accuracy: behavioral and neuroimaging evidence. *Curr. Dir. Psychol. Sci.* 16, 213–218.

Kensinger, E. A. (2009). Remembering the details: effects of emotion. *Emot. Rev.* 1, 99–113.

Kensinger, E. A., Addis, D. R., and Atapattu, R. K. (2011). Amygdala activity at encoding corresponds with memory vividness and with memory for select episodic details. *Neuropsychologia* 49, 663–673.

Kensinger, E. A., and Corkin, S. (2003). Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? *Mem. Cognit.* 31, 1169–1180.

Kensinger, E. A., and Corkin, S. (2004). Two routes to emotional memory: distinct neural processes for valence and arousal. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3110–3115.

Kensinger, E. A., Geoff-Eaton, R. J., and Schacter, D. L. (2005). Memory for specific visual details can be enhanced by negative arousing content. *J. Mem. Lang.* 54, 99–112.

Kensinger, E. A., and Schacter, D. L. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *J. Neurosci.* 26, 2564–2570.

Kent, B. A., and Brown, T. H. (2012). Dual functions of the perirhinal cortex in fear conditioning. *Hippocampus* 22, 2068–2079.

Knight, M., Seymour, T. L., Gaunt, J. T., Baker, C., Nesmith, K., and Mather, M. (2007). Aging and goal-directed emotional attention: distraction reverses emotional biases. *Emotion* 7, 705–714.

Krettek, J. E., and Price, J. L. (1977). Projections from the amygdaloid complex and adjacent olfactory structures to the entorhinal cortex and to the subiculum in the rat and cat. *J. Comp. Neurol.* 172, 723–752.

LaBar, K. S. (2007). Beyond fear emotional memory mechanisms in the human brain. *Curr. Dir. Psychol. Sci.* 16, 172–177.

LaBar, K. S., Mesulam, M., Gitelman, D. R., and Weintraub, S. (2000). Emotional curiosity: modulation of visuospatial attention by arousal is preserved in aging and early-stage Alzheimer's disease. *Neuropsychologia* 38, 1734–1740.

Lacy, J. W., and Stark, C. E. (2012). Intrinsic functional connectivity of the human medial temporal lobe suggests a distinction between adjacent MTL cortices and hippocampus. *Hippocampus* 22, 2290–2302.

Lambon, R. M. A., Sage, K., Jones, R. W., and Mayberry, E. J. (2010). Coherent concepts are computed in the anterior temporal lobes. *Proc. Natl. Acad. Sci. U.S.A.* 107, 2717–2722.

Lavenex, P., and Amaral, D. G. (2000). Hippocampal-neocortical interaction: a hierarchy of associativity. *Hippocampus* 10, 420–430.

Levine, L. J., and Edelstein, R. S. (2009). Emotion and memory narrowing: a review and goal-relevance approach. *Cogn. Emot.* 23, 833–875.

MacKay, D. G., Shafto, M., Taylor, J. K., Marian, D. E., Abrams, L., and Dyer, J. R. (2004). Relations between emotion, memory and attention: evidence from taboo Stroop, lexical decision, and immediate memory tasks. *Mem. Cognit.* 32, 474–488.

Madan, C. R., Caplan, J. B., Lau, C. S. M., and Fujiwara, E. (2012). Emotional arousal does not enhance association-memory. *J. Mem. Lang.* 66, 695–716.

Maren, S., and Fanselow, M. S. (1985). Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation *in vivo*. *J. Neurosci.* 15, 7548–7564.

Mather, M. (2007). Emotional arousal and memory binding: an object-based framework. *Perspect. Psychol. Sci.* 2, 33–52.

Mather, M., and Knight, M. R. (2006). Angry faces get noticed quickly: threat detection is not impaired among older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci* 61, 54–57.

Mather, M., Mitchell, K. J., Raye, C. L., Novak, D. L., Greene, E. J., and Johnson, M. K. (2006). Emotional arousal can impair feature binding in working memory. *J. Cogn. Neurosci.* 18, 614–625.

Mather, M., and Nesmith, K. (2008). Arousal-enhanced location memory for pictures. *J. Mem. Lang.* 58, 449–464.

Mather, M., and Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.* 6, 114–133.

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn. Sci. (Regul. Ed.)* 11, 126–135.

McGaugh, J. (2000). Memory – a century of consolidation. *Science* 287, 248–251.

McGaugh, J. (2004). The amygdala modulates the consolidation of memories and emotionally arousing experiences. *Annu. Rev. Neurosci.* 27, 1–28.

Mickes, L., Johnson, E., and Wixted, J. T. (2010). Continuous recollection vs. unitized familiarity in associative recognition. *J. Exp. Psychol. Learn. Mem. Cogn.* 36, 843–863.

Mickley Steinmetz, K. R., Addis, D. R., and Kensinger, E. A. (2010). The effect of arousal on the emotional memory network depends on valence. *Neuroimage* 53, 318–324.

Montaldi, D., and Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus* 20, 1291–1314.

Morris, J. S., Friston, K. J., Büchel, C., Frith, C. D., Young, A. W., Calder, A. J., et al. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 121, 47–57.

Müller, G. E., and Pilzecker, A. (1900). Experimentelle Beiträge zur Lehre vom Gedächtnis. *Z. Psychol. Ergänzungsband* 1, 1–300.

Murray, B. D., and Kensinger, E. A. (2012). The effects of emotion and encoding strategy on associative memory. *Mem. Cognit.* 40, 1056–1069.

Murray, B. D., and Kensinger, E. A. (2013). "Mental integration of emotional and non-emotional verbal pairs is supported by dissociable neural regions at encoding and retrieval," in *Poster Presented at the Cognitive Neuroscience Society Annual Meeting*, San Francisco, CA.

Nashiro, K., and Mather, M. (2010). How arousal affects older and younger adults' memory binding. *Exp. Aging Res.* 37, 108–128.

Neisser, U., and Harsch, N. (1992). "Phantom flashbulbs: false recollections of hearing the news about challenger," in *Affect and Accuracy in Recall: Studies of "Flashbulb" Memories*, eds E. Winograd and U. Neisser (New York: Cambridge University Press), 9–31.

Nummenmaa, L., Hyönä, J., and Calvo, M. G. (2006). Eye movement

assessment of selective attentional capture by emotional pictures. *Emotion* 6, 257–268.

Ochsner, K. N. (2000). Are affective events richly "remembered" or simply familiar? The experience and process of recognizing feelings past. *J. Exp. Psychol. Gen.* 129, 242–261.

Öhman, A., Flykt, A., and Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *J. Exp. Psychol. Gen.* 130, 466–478.

Öhman, A., and Mineka, S. (2001). Fear, phobias, and preparedness: toward and evolved module of fear and fear learning. *Psychol. Rev.* 108, 483–522.

Okada, G., Okamoto, Y., Kunisato, Y., Aoyama, S., Nishiyama, Y., Yoshimura, S., et al. (2011). The effect of negative and positive emotionality on associative memory: an fMRI study. *PLoS ONE* 6:e24862. doi:10.1371/journal.pone.0024862

Perugini, A., Laing, M., Berretta, N., Aicardi, G., and Bashir, Z. I. (2012). Synaptic plasticity from amygdala to perirhinal cortex: a possible mechanism for emotional enhancement of visual recognition memory? *Eur. J. Neurosci.* 36, 1–7.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* 14, 198–202.

Phelps, E. A., and Sharot, T. (2008). How (and why) emotion enhances the subjective sense of recollection. *Curr. Dir. Psychol. Sci.* 17, 147–152.

Pierce, B. H., and Kensinger, E. A. (2011). Effects of emotion on associative recognition: valence and retention interval matter. *Emotion* 11, 139–144.

Pilgrim, L. K., Murray, J. G., and Donaldson, D. I. (2012). Characterizing episodic memory retrieval: electrophysiological evidence for diminished familiarity following unitization. *J. Cogn. Neurosci.* 24, 1671–1681.

Pitkänen, A., Pikkarainen, M., Nurminen, N., and Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat: a review. *Ann. N. Y. Acad. Sci.* 911, 369–391.

Quamme, J. R., Yonelinas, A. P., and Norman, K. A. (2007). Effect of unitization on associative recognition in amnesia. *Hippocampus* 17, 192–200.

Reisberg, D., and Heuer, F. (2004). "Memory for emotional events," in *Memory and Emotion*, eds D. Reisberg and P. Hertel (New York: Oxford University Press), 3–41.

Richardson, M. P., Strange, B. A., and Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nat. Neurosci.* 7, 278–285.

Russell, J. A. (1980). A circumplex model of affect. *J. Pers. Soc. Psychol.* 39, 1161–1178.

Saksida, L. M., and Bussey, T. J. (2010). The representational-hierarchical view of amnesia: translation from animal to human. *Neuropsychologia* 48, 2370–2384.

Savander, V., LeDoux, J. E., and Pitkänen, A. (1997). Interamygdaloid projections of the basal and accessory basal nuclei of the rat amygdaloid complex. *Neuroscience* 76, 725–735.

Sharot, T., Delgado, M. R., and Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nat. Neurosci.* 7, 1376–1380.

Sharot, T., and Phelps, E. A. (2004). How arousal modulates memory: disentangling the effects of attention and retention. *Cogn. Affect. Behav. Neurosci.* 4, 294–306.

Sharot, T., and Yonelinas, A. P. (2008). Differential time-dependent effects of emotion on recollective experience and memory for contextual information. *Cognition* 106, 538–547.

Shi, C. J., and Cassell, M. D. (1999). Perirhinal cortex projections to the amygdaloid complex and hippocampal formation in the rat. *J. Comp. Neurol.* 406, 299–328.

Skipper, L. M., Ross, L. A., and Olson, I. R. (2011). Sensory and semantic category subdivisions within the anterior temporal lobes. *Neuropsychologia* 49, 3419–3429.

Squire, L. R. (1992). Declarative and nondeclarative memory: multiple brain systems supporting learning and memory. *J. Cogn. Neurosci.* 4, 232–243.

Squire, L. R., Wixted, J. T., and Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nat. Rev. Neurosci.* 8, 872–883.

Squire, L. R., and Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science* 253, 1380–1386.

Staresina, B. P., and Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *J. Neurosci.* 26, 9162–9172.

Staresina, B. P., and Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *J. Cogn. Neurosci.* 20, 1478–1489.

Staresina, B. P., and Davachi, L. (2010). Object unitization and associative memory formation are supported by distinct brain regions. *J. Neurosci.* 30, 9890–9897.

Suzuki, W. A. (2010). Untangling memory from perception in the medial temporal lobe. *Trends Cogn. Sci. (Regul. Ed.)* 14, 195–200.

Suzuki, W. A., Miller, E. K., and Desimone, R. (1997). Object and place memory in the macaque entorhinal cortex. *J. Neurophysiol.* 78, 1062–1081.

Szpunar, K. K., Addis, D. R., and Schacter, D. L. (2012). Memory for emotional simulations: remembering a rosy future. *Psychol. Sci.* 23, 24–29.

Talarico, J. M., and Rubin, D. C. (2003). Confidence, not consistency, characterizes flashbulb memories. *Psychol. Sci.* 14, 455–461.

Vuilleumier, P. (2005). How brains beware: neural mechanisms of emotional attention. *Trends Cogn. Sci.* 9, 585–594.

Vuilleumier, P., Armony, J. L., Driver, J., and Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron* 30, 829–841.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* 7, 1271–1278.

Waring, J. D., and Kensinger, E. A. (2011). How emotion leads to selective memory: neuroimaging evidence. *Neuropsychologia* 49, 1831–1842.

Windmann, S., Urbach, T. P., and Kutas, M. (2002). Cognitive and neural mechanisms of decision biases in recognition memory. *Cereb. Cortex* 12, 808–817.

Wixted, J. T. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychol. Rev.* 114, 152–176.

Wollen, K. A., Webber, A., and Lowry, D. H. (1972). Bizarreness versus interaction of mental images as determinants of learning. *Cogn. Psychol.* 3, 518–523.

Xu, Y., and Chun, M. M. (2006). Dissociable neural mechanisms supporting visual sort-term memory for objects. *Nature* 440, 91–95.

Yonelinas, A. P. (1994). Receiver-operating characteristics in recognition memory: evidence for dual-process model. *J. Exp. Psychol. Learn. Mem. Cogn.* 20, 1341–1354.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517.

Zimmerman, C. A., and Kelley, C. M. (2010). "I'll remember this!" Effects of emotionality on memory predictions versus memory performance. *J. Mem. Lang.* 62, 240–253.

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The effect of retrieval focus and emotional valence on the inferior frontal cortex activity during autobiographical recollection

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Although available evidence points to a role of the inferior frontal cortex (IFC) in both emotion processing and autobiographical memory (AM) recollection, it is unclear what the role of this region is in emotional AM recollection. The present study investigated whether IFC activity can be influenced by manipulations of the retrieval focus (emotional vs. non-emotional) and whether this influence is similar for AMs with positive and negative emotional valence. Participants were asked to focus either on emotional (*Emotion* condition) or on non-emotional contextual (*Context* condition) details during the elaboration of positive and negative AMs, while fMRI data were collected. The study yielded two main findings: (1) Focusing on Emotion compared to Context during AM recollection was associated with increased activity in bilateral IFC, for positive AMs, whereas negative AMs produced similarly high IFC activity during Emotion and Context conditions; (2) There was a hemispheric dissociation in the IFC linked to the experiencing of emotion and the focus of AM recollection, such that the left IFC activity correlated positively with the subjective re-experience of emotion during the Emotion condition, whereas the right IFC activity correlated negatively with the subjective re-experience of emotion during the Context condition, for both positive and negative AMs. Overall, the present findings suggest that IFC's involvement during the recollection of emotional AMs is susceptible to manipulations of the retrieval focus only in the case of positive AMs, and that this region plays a role in both the enhancement and inhibition of emotional experience during AM recollection.

Keywords: episodic memory, emotional valence, retrieval goal, inferior frontal gyrus, insula

INTRODUCTION

There is considerable evidence that the inferior frontal cortex (IFC) plays an important role in language (Poldrack et al., 1999), cognitive control (Badre, 2008), memory (Thompson-Schill et al., 1997; Fletcher and Henson, 2001), emotion processing (Wager et al., 2008; Lindquist et al., 2012), and emotion regulation (Ochsner et al., 2012), possibly through its involvement in operations such as language unification (Hagoort, 2005), controlled retrieval (Badre and Wagner, 2007), selection among competing alternatives (Thompson-Schill et al., 1999; Moss et al., 2005; Grindrod et al., 2008), integration of information (Fuster, 2002), and response inhibition (Aron et al., 2004). Of particular interest for the present investigation, evidence derived from separate lines of research points to a pivotal role of the IFC in memory retrieval (Greenberg et al., 2005; Badre and Wagner, 2007) and in emotion processing (Wager et al., 2008; Lindquist et al., 2012). The goal of the present investigation is to elucidate the role of IFC in the retrieval of emotional autobiographical memories (AMs) according to the retrieval focus and the valence of memories.

Functional neuroimaging evidence from separate lines of investigations suggests a role of the IFC in both the enhancement and inhibition of emotion processing (Hooker and Knight, 2006; Dolcos et al., 2011; Ochsner et al., 2012; Iordan et al., 2013). Studies investigating the influence of emotion on memory have provided evidence for a role of the IFC in enhancing the effect of emotion on memory formation (Dolcos et al., 2004) and in diminishing the impact of negative goal-irrelevant emotional distraction on working memory (Dolcos et al., 2006, 2008, 2013). Studies investigating the neural correlates of emotion control have pointed to the IFC's contribution to voluntary up- and down-regulation of emotion (Ochsner et al., 2004; Kim and Hamann, 2007). The evidence from these investigations is based nearly exclusively on externally triggered emotions in experimental settings (e.g., by viewing emotional pictures), most of the time negative, rather than on internally triggered emotions (e.g., recall of emotional personal memories). Here, we investigate the role of IFC in the processing of internally triggered emotions associated with the recollection of emotional AMs.

Internally triggered emotions are more ecologically valid and can generate stronger emotional responses than those produced by external stimulation in experimental settings (Salas et al., 2012). Also, the former are at the basis of maintaining affective disorders,

such as depression and post-traumatic stress disorder (Brewin et al., 1999; Rubin et al., 2008), which are characterized by an increased focus toward negative personal memories and/or inhibition of positive ones (Werner-Seidler and Moulds, 2011). Recollection of emotional AMs has been linked, among other brain regions, to the involvement of IFC (Markowitsch et al., 2000). The more ventral portion of the IFC, part of the temporo-frontal junction interconnected through the ventral branch of the uncinate fascicle, has been attributed a crucial role in "synchronizing emotional and factual components of the personal past" during remembering (Brand and Markowitsch, 2008; p. 326; Markowitsch, 1995; Brand and Markowitsch, 2006). IFC's involvement has also been found in "non-emotional" AM studies (Conway et al., 1999; Piolino et al., 2004; Greenberg et al., 2005; Daselaar et al., 2008). Typically, this region has been associated with successful memory retrieval, which involves strategic search and selection of appropriate information and monitoring of the veracity and cohesiveness of the recollected memory (Svoboda et al., 2006; Badre and Wagner, 2007). It is not clear, however, whether IFC's involvement during the recollection of emotional AMs can be influenced by the focus of retrieval (emotional vs. non-emotional), and whether this influence is similar for positive and negative AMs. Given that positive and negative AMs may be governed by different mechanisms and lead to different outcomes (Denkova et al., 2012), and that IFC appears to be more involved for negative AMs (Markowitsch et al., 2003), it is important to clarify the role of emotional valence in the retrieval of emotional AMs. While negative memories have received, overall, much more attention in the literature, there is also evidence highlighting the importance of positive memories in promoting personal self-esteem and overall positive mindset (Diener and Seligman, 2002; Fredrickson, 2004; D'Argembeau and Van der Linden, 2008; Denkova et al., 2012), and their beneficial effects in depressed people (Dalgleish et al., 2013).

The main goal of the present study was to investigate the involvement of the IFC during the recollection of emotional AMs, linked to the focus of retrieval (emotional vs. non-emotional) and the valence of memories (positive vs. negative). For this purpose, fMRI data were recorded while participants were cued to focus either on emotional (*Emotion* condition) or on non-emotional contextual (*Context* condition) details, during elaboration of highly emotional positive and negative AMs. Based on the extant evidence, we made the following predictions. General sensitivity of the IFC to manipulations of the retrieval focus should be reflected in differential engagement of this region in the *Emotion* and *Context* conditions, for both positive and negative AMs, such that increased IFC activity during the *Emotion* condition would be associated with enhanced emotional experience. However, it is also expected that retrieval focus may also result in specific sensitivity of the IFC response linked to the valence of AMs, possibly reflecting the enhancement of positive emotions and the inhibition of negative emotions.

MATERIALS AND METHODS

PARTICIPANTS

Analyses were performed on data from 17 right-handed native English speaking young adults (6 men; age range 18–46, mean = 26.06 years, SD = 7.20), who provided written informed consent and received payment for their participation. The experimental protocol was approved by the Institutional Health Research Ethics Board.

COLLECTION AND SELECTION OF EMOTIONAL AUTOBIOGRAPHICAL MEMORIES

Personal memories were elicited from each participant during an interview performed approximately 5 weeks prior to the fMRI session using an autobiographical memory questionnaire (AMQ) (Denkova et al., 2012). The AMQ comprised a list of 115 verbal cues for distinct life events (e.g., "the birth of a family member," "being hospitalized"); for each of them, participants were asked to remember a unique episode from their life and to provide a brief description of the memory, which was then used as a personalized memory cue during the fMRI scanning. Phenomenological characteristics of each event were assessed by asking the participants to date the memory and rate it on several Likert scales including Emotional Valence (using a 7-point scale: −3 = very negative, 0 = neutral, and +3 = very positive), Emotional Intensity, Personal Significance, Vividness, the amount of Contextual Details, and the Frequency of Retrieval (all of the latter used a 7-point scale: 1 = not at all, 7 = extremely). For each participant, we selected the 40 most emotional memories (20 positive and 20 negative), based on the emotional ratings. Half of the selected memories, with an equal proportion of positive and negative, were assigned to the *Emotion* condition, and the other half of AMs were assigned to the *Context* condition.

fMRI TASKS

The autobiographical memory tasks

(i) In the *Emotion* focus condition, participants were instructed to remember the specific event and focus on the emotional aspects of their memories, including associated sensations and feelings (e.g., butterflies in the stomach, palpitations). (ii) In the *Context* focus condition, participants were instructed to remember the specific event and focus on the contextual aspects of their memories, by retrieving as many contextual details as possible (e.g., about where and when the event occurred). Each memory cue was preceded either by the instruction cue "Remember Emotion" (for the Emotion condition), or "Remember Context" (for the Context condition). After recollection, each event was rated on three five-point Likert scales including Emotional Intensity, Vividness, and Reliving (1 = very low; 5 = very high).

The semantic memory control task

In line with other AM studies (Greenberg et al., 2005; Young et al., 2013), we also used a control condition involving semantic memory (SM) retrieval, such as the generation of exemplars from different semantic categories (e.g., sports, vegetables) (Battig and Montague, 1969). Each semantic category cue was preceded by the instruction cue "Generate Examples." To be consistent with AM conditions, each exemplar generation was rated on three five-point Likert scales including Vividness, Difficulty of the task, and approximate Number of the recalled items.

fMRI DESIGN

The AM and SM conditions had the same general structure (Denkova et al., 2011). Each trial began with an instruction screen

for 2 s, immediately followed by a memory cue for 4 s. After the cue offset, a fixation screen was presented for 10 s during which participants elaborated their personal memories or generated exemplars. The end of the retrieval period was marked by an instruction screen for upcoming ratings, for 1.5 s. Then, each of the three ratings was presented for 2.5 s and in a counterbalanced order across trials. The ratings were followed by an inter-trial interval of variable duration (2–9 s, average = 6 s), before the beginning of the next trial.

MRI DATA COLLECTION

MRI data were recorded using a 1.5-T Siemens Sonata scanner. The anatomical images were 3D MPRAGE anatomical series [repetition time (TR) = 1600 ms, echo time (TE) = 3.82 ms, field of view (FOV) = 256 mm × 256 mm, number of slices = 112, voxel size = 1 mm × 1 mm × 1 mm]. The functional images consisted of series of images acquired axially using an echoplanar sequence (TR = 2000 ms, TE = 40 ms, FOV = 256 mm × 256 mm, number of slices = 28, voxel size = 4 mm × 4 mm × 4 mm).

fMRI DATA ANALYSIS

Statistical analyses, performed with SPM2 (Statistical Parametric Mapping), were preceded by the following pre-processing steps: Quality Assurance, TR Alignment, Motion Correction, Coregistration, Normalization, and Smoothing (8 mm full-width half maximum isotropic Kernel). At the individual level, each event was modeled by the canonical hemodynamic response function (*hrf*) and its temporal derivate. The *hrf* was time-locked to 2 s (1 TR) following the onset of the memory cues, in the Emotion and Context AM conditions, and 1 s (0.5 TR) after the onset of the category cue, in the SM condition to allow time for reading the cues. This procedure was guided by the present RT data, which showed that the recognition of the AM cue and beginning of retrieval occurred at an average RT of 1.67 s (±0.44), and the beginning of the exemplar generation in the SM condition occurred at an average RT of 1.03 s (±0.40). This procedure allows comparisons of the fMRI signal associated with AM and SM retrieval, by accounting for differences in the timing of retrieval operations and memory identification, and is consistent with the procedure used in previous neuroimaging studies of AM retrieval (Addis et al., 2007). Individual contrasts were computed directly between the different AM event types (e.g., Emotion Positive vs. Context Positive, Emotion Negative vs. Context Negative). These individual contrasts were then entered into group-level *t* tests, to perform random-effects analyses.

The effects of retrieval focus were investigated by comparing AMs with Emotion focus and AMs with Context focus separately for positive and negative AMs. The interaction effects of retrieval focus and valence were investigated using paired *t* tests [e.g., (Emotion Positive vs. Context Positive) vs. (Emotion Negative vs. Context Negative)], whose outputs were inclusively masked with the direct contrast of interest (e.g., Emotion Positive vs. Context Positive), to ensure that the interaction difference is due to an existing increased difference in the contrasts of interest. Finally, to investigate whether activity in IFC according to the retrieval focus and valence is linked to the self-reported re-experience of emotion, linear regression analyses were performed between overall IFC activity in each AM condition (i.e., Emotion Positive vs. baseline; Emotion Negative vs. baseline; Context Positive vs. baseline and Context Negative vs. baseline) and the corresponding self-reported emotional ratings.

Activity in regions of interest was investigated using adapted anatomical masks from the Wake Forest University Pick Atlas toolbox. The threshold was set up at $p < 0.001$ for the direct contrasts and at $p < 0.05$ for the interactions and correlations; the extent threshold was of five contiguous voxels in all analyses. The interaction maps were masked inclusively with the corresponding direct

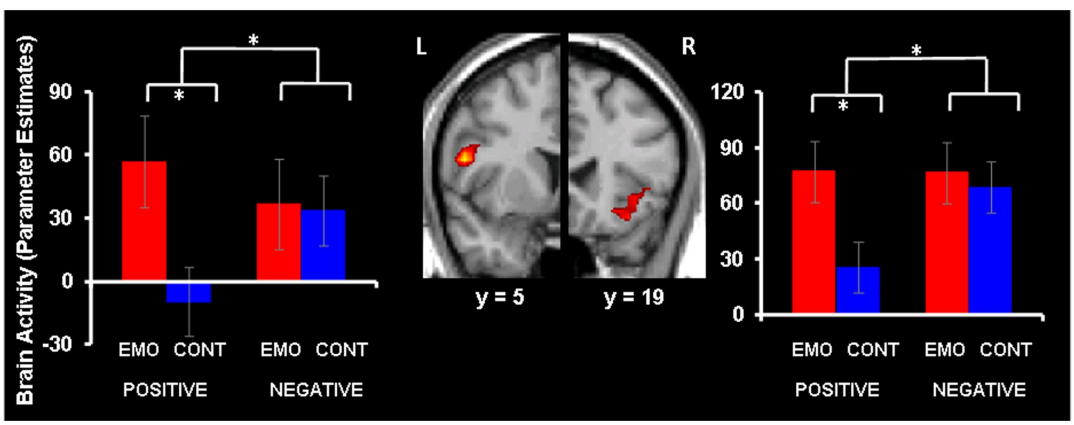


FIGURE 1 | Increased IFC activity for emotion compared to context focus for positive AMs. Focusing on Emotion (EMO) compared to focusing on Context (CONT) led to increased activity in bilateral IFC (red blobs) for positive AMs, whereas negative AMs produced similar IFC activity during EMO and CONT conditions. The interaction map is superimposed on a high resolution brain image displayed in a coronal view (with *y* indicating the Talairach coordinates on the anterior-posterior axis of the brain). For illustration purpose, the interaction map set up at $p < 0.05$ is inclusively masked with the direct contrast set up at $p < 0.05$; the effects are also observed when the mask is set up at $p < 0.001$ (**Table 1**). The bar graphs represent the contrast estimates extracted from representative voxels in the left and right IFC, respectively. The error bars correspond to the standard errors of the means. L, Left; R, Right.

contrast set up at $p < 0.001$. Activations in other brain regions, including basic emotion and memory-related medial temporal lobe (MTL) brain areas are reported in a previous report (Denkova et al., 2013). In short, these findings revealed increased activity for positive AMs in the amygdala (AMY) and hippocampus, and in other brain regions, including lateral temporal and prefrontal cortices. Given the similarity of patterns observed in the AMY and IFC, we further investigated the relationship between activity in these two regions, by performing linear regression analyses between IFC activity for Emotion vs. Context contrast (extracted from peak voxels showing significant differences in activation, in the right and left IFC, BA 47) and brain activity in the AMY.

RESULTS

BEHAVIORAL RESULTS

Increased re-experiencing of emotion during emotion focused retrieval for both positive and negative AMs

Repeated-measures ANOVA revealed a focus × ratings interaction [$F_{(1,16)} = 4.12$, $p = 0.03$], driven by an increase only for the emotional intensity ratings of AMs retrieved with an emotional focus and the absence of significant differences in the other ratings (Reliving and Vividness ratings). The increase was significant for both positive (3.21 vs. 3.03, $p = 0.02$) and negative (3.38 vs. 3.07, $p = 0.003$) AMs.

fMRI RESULTS

Increased IFC activity for emotion compared to context focus for positive AMs

Focusing on Emotion compared to Context led to increased activity in bilateral IFC (BAs 44 and 47) for positive memories, but similarly high IFC engagement under the Emotion and Context foci was observed for negative AMs (see **Figure 1** and **Table 1**). These effects were confirmed by a repeated-measures ANOVA performed on the extracted signal, which, in the left IFC (BA 44), revealed a significant valence × focus interaction [$F_{(1,16)} = 15.93$, $p = 0.001$]. This interaction was driven by a significant increase in the Emotion compared to the Context condition, for positive ($p < 0.001$) but not for negative ($p = 0.80$) AMs. Similarly, the effect in the right IFC (BA 47) was confirmed by a repeated-measures ANOVA revealing a significant valence × focus interaction [$F_{(1,16)} = 7.26$, $p = 0.015$], which was driven by a significant increase in the Emotion compared to the Context condition for positive ($p < 0.001$) but not for negative ($p = 0.50$) AMs.

Hemispheric dissociation in the IFC linked to the experiencing of emotion and the focus of AM recollection

Brain-behavior correlation analyses revealed opposing patterns of co-variation between activity in the left (showing positive co-variation) and right (showing negative co-variation) IFC and emotional ratings, for Emotion and Context focus, respectively (**Figure 2** and **Table 1**). These effects were common for both positive and negative AMs, as revealed by the conjunction analyses of *Emotion* Positive ∩ *Emotion* Negative and of *Context* Positive ∩ *Context* Negative conditions, respectively. Specifically, activity in a left IFC (BA 47) area, extending to the insula, positively correlated with self-reported re-experience of emotion, for both positive and negative AMs, for the Emotion but not for the Context condition. Similar effects were observed in a more dorsal left IFC (BA 46) area, but they were not specific to the Emotion condition (**Table 1**). On the other hand, activity in a right IFC (BA 47) area negatively correlated with self-reported re-experience of emotion, for both positive and negative AMs, for the Context but not for the Emotion condition. Overall, these findings suggest a hemispheric dissociation in the IFC linked to the experiencing of emotion and the focus of AM recollection, with the left IFC (BA 47) activity showing specific positive correlations with the subjective re-experience of emotion during the Emotion condition, and the right IFC (BA 47) activity showing specific negative correlations with the subjective re-experience of emotion during the Context condition.

Further analyses revealed positive co-variations between activity in the IFC and the AMY (**Figure 3**). For positive AMs, positive co-variations were observed between activity in the right IFC and the right ($x = 24$, $y = 3$, $z = -14$; $R = 0.67$, $p = 0.002$) and left ($x = -32$, $y = -8$, $z = -13$; $R = 0.79$, $p < 0.001$) AMY, as well as between activity in the left IFC and the right ($x = 32$, $y = -1$,

Table 1 | Significant activations and correlations linked to the retrieval focus and the emotional valence of memories.

IFC (BA)	Side	Talairach coordinates			*t* Score	Cluster size
		x	*y*	*x*		
DIRECT CONTRASTS						
Emotion Positive vs. Context Positive						
IFG (44)	L	−55	12	10	4, 91	8
IFG (47)	R	40	27	−1	4, 90	22
IFG (47)	L	−36	19	−8	4, 85	28
INTERACTIONS						
(Emotion Positive vs. Context Positive) vs. (Emotion Negative vs. Context Negative)						
IFG (44)	L	−55	12	14	3, 99	7
IFG (47)	R	32	23	−15	2, 69	12
CORRELATIONS						
A. Positive correlations						
Emotion (Emotion Positive ∩ Emotion Negative)						
IFG (47)	L	−32	15	−11	3, 13/2, 45	7
IFG (46)	L	−48	28	17	2, 14/2, 07	6
Context (Context Positive ∩ Context Negative)						
IFG (46)	L	−51	32	9	2, 61/2, 04	12
B. Negative correlations						
Context (Context Positive ∩ Context Negative)						
IFG (47)	R	24	35	−8	3, 42/2, 01	5

Significant activations and correlations resulting from ROI analyses are reported. For direct contrasts, a threshold of p < 0.001 was used. For interactions, a threshold of p < 0.05 was used and further inclusively masked with the corresponding direct contrast set up at p < 0.001. For correlations, a threshold of p < 0.05 was used, and the overlaps between positive and negative AMs within each focus are presented. A cluster size of five contiguous voxels was used for all analyses. IFG, inferior frontal gyrus; BA, Brodmann's area; L, Left, R = Right.

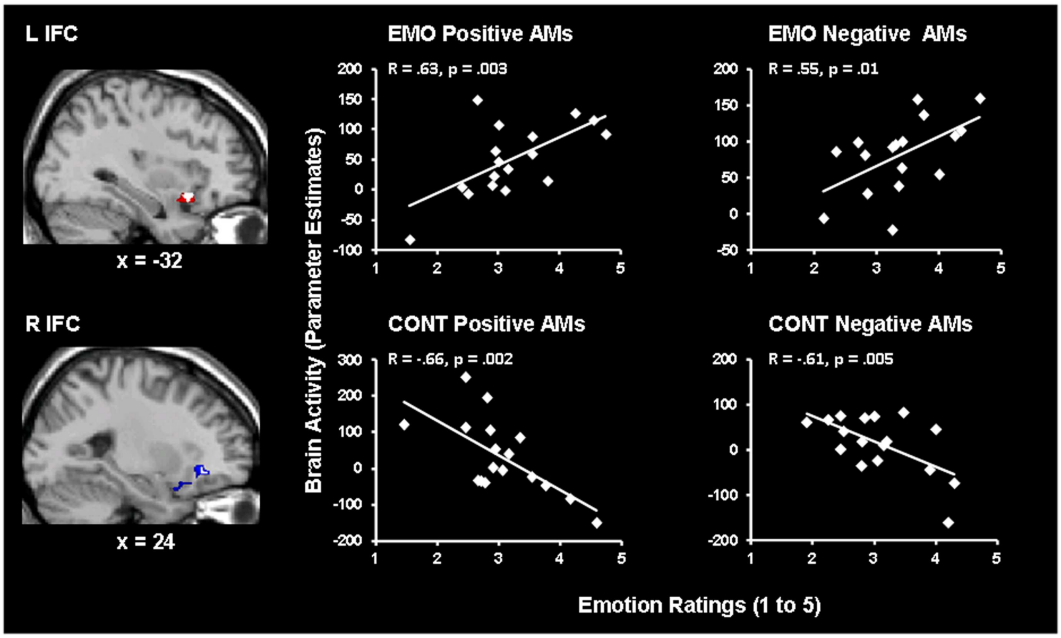


FIGURE 2 | Hemispheric dissociation in the IFC linked to the experiencing of emotion and the focus of AM recollection. Activity in the left IFC correlated positively with emotional ratings in the Emotion (EMO) condition, for both positive and negative AMs, whereas activity in the right IFC correlated negatively with emotional ratings in the Context (CONT) focus, for both positive and negative AMs. The correlation maps in the left and right IFC are superimposed on high resolution brain images displayed in sagittal views (with *x* indicating the Talairach coordinates for the left/right hemispheres of the brain). The white blobs represent the areas where there are overlapping voxels for both positive and negative AMs, which are superimposed on larger areas showing positive (red) or negative (blue) co-variations either for positive or for negative AMs. The scatterplots are based on contrast estimates of the IFC activity for each condition, as extracted from the peak voxels of the areas showing the co-variation with the corresponding emotional ratings. L, Left; R, Right.

$z = -17$; $R = 0.56$, $p = 0.01$) and left ($x = -28$, $y = -8$, $z = -13$; $R = 0.66$, $p = 0.002$) AMY. Of note, portions of the AMY showing positive co-variation with the IFC overlapped with portions of the AMY areas showing significant increase in activity for positive memories with Emotion vs. Context focus reported in Denkova et al. (2013) (**Figure 3**). Interestingly, similar patterns of positive co-variations between activity in the IFC and AMY were also observed for negative memories, despite the absence of significant differences in the IFC activity between Emotion and Context. Namely, activity in the right IFC positively correlated with activity in the right ($x = 20$, $y = -1$, $z = -10$; $R = 0.87$, $p < 0.001$) and left ($x = -32$, $y = -4$, $z = -10$; $R = 0.78$, $p = 0.001$) AMY, and activity in the left IFC positively correlated with activity in the right ($x = 20$, $y = -1$, $z = -10$; $R = 0.82$, $p < 0.001$) and left ($x = -32$, $y = -8$, $z = -13$; $R = 0.69$, $p = 0.001$) AMY. An overlap between the correlation and activation patterns was observed only in the left AMY (see **Figure 3**), given that significant differences in activity between Emotion and Context for negative AMs was revealed only in the left AMY (Denkova et al., 2013).

DISCUSSION

The present study investigated the IFC's involvement during AM recollection, as a function of the retrieval focus and emotional valence. There were two main findings, which are discussed in turn below.

INCREASED IFC ACTIVITY FOR EMOTION COMPARED TO CONTEXT FOCUS FOR POSITIVE AMs

This finding is overall consistent with previous investigations linking IFC's involvement to enhanced encoding of emotional items (Dolcos et al., 2004), retrieval of emotional AMs (Markowitsch et al., 2000), as well as voluntary up-regulation of positive emotions (Kim and Hamann, 2007). Importantly, the present finding extends the available evidence by showing that activity in the IFC is susceptible to manipulations of the retrieval focus only during the recollection of positive AMs, showing increased activity during retrieval of positive AMs with an emotion focus and decreased activity when the focus is on other non-emotional contextual details. Keeping in mind that IFC is a heterogeneous structure with distinct subregions (Petrides and Pandya, 2002), the increased activity in different IFC subregions in the present study could be interpreted as follows. Given its role in the subjective experience of emotion (Wager et al., 2008), increased activity in BA 47 could reflect the integration and enhancement of emotional experience during autobiographical retrieval. This interpretation is further supported by the positive relationship between activity in the IFC and the AMY, which suggests that IFC's involvement reflects the integration of emotional information triggered by the AMY and further enhancement of the emotional experience during remembering of AMs with Emotion focus. Given its general role in language production and in inner speech (McGuire et al., 1996; Baciu et al., 1999), particularly during self-referential activities

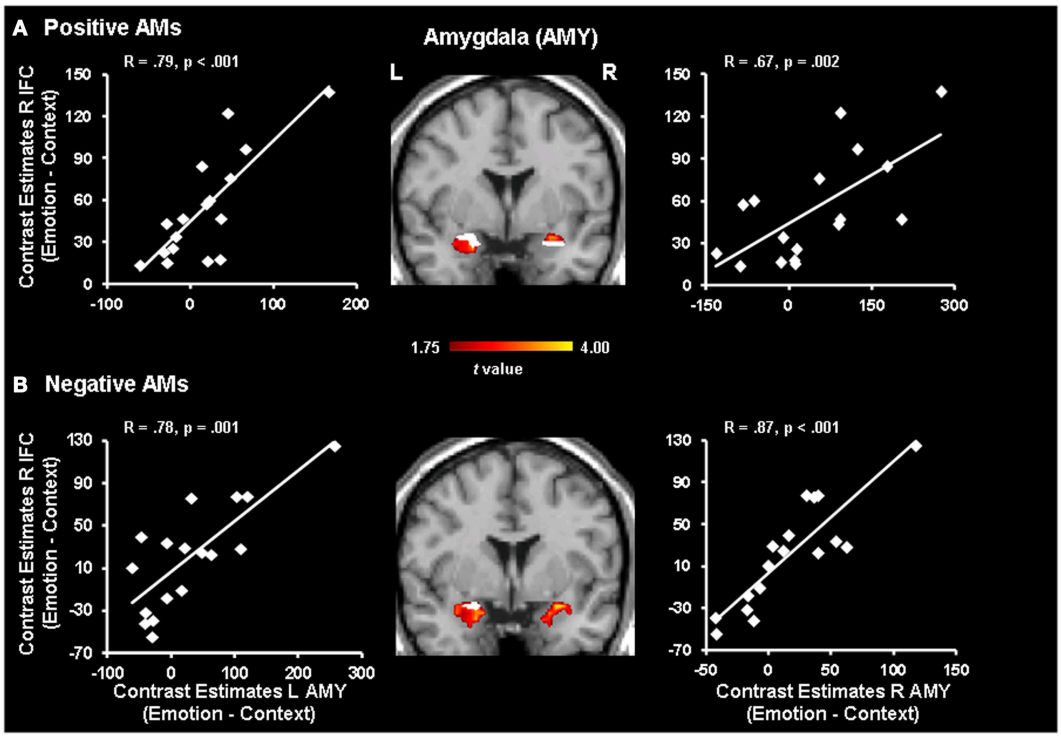


FIGURE 3 | Positive correlations between activity in the IFC and the AMY. Activity in the right Inferior Frontal Cortex (IFC) positively correlated with activity in the left and right AMY (red blobs) for positive **(A)** and negative **(B)** AMs, despite the absence of significant differences in the IFC activity between Emotion and Context for the latter. Portions of the AMY showing positive co-variations with the IFC also overlapped (white blobs) with AMY areas showing significant increase in activity for Emotion vs. Context focus. The gradient color bar starts at $p < 0.05$ ($t = 1.75$). Similar patterns of correlations were observed in the left IFC (not shown, see text). The scatterplots are based on contrast estimates for Emotion vs. Context extracted from the peak voxel of the areas showing the co-variation with AMY activity. L, left; R, right.

(Morin and Michaud, 2007), of which autobiographical remembering is an essential part, increased activity in the left BA 44 could be linked to a more general reliance on covert speech mechanisms during recollection of positive AMs with Emotion focus.

The present findings suggest that, compared to the emotion focused positive recollections, context focused positive recollections appear to easily lose their emotionality in the absence of an explicit focus on the (re)experienced emotions. This provides a possible explanation for evidence showing that recalling positive memories cannot always reverse negative mood in depressed people (Joormann et al., 2007), and is consistent with recent evidence from clinical studies suggesting that positive memories could potentially alleviate negative mood depending on the way they are processed (Werner-Seidler and Moulds, 2012; Dalgleish et al., 2013). This finding is also consistent with evidence from healthy participants showing that, unlike negative AMs whose retrieval has a strong direct effect on the post-retrieval negative emotional state, retrieval of positive AMs has a weaker and indirect effect on the positive state (Denkova et al., 2012).

In contrast with positive AMs, remembering negative AMs showed similarly high IFC involvement, regardless of the focus of retrieval. This could reflect the engagement of selection and inhibitory operations, necessary to evaluate the relevance of negative emotional information according to the current retrieval goals, and to incorporate and enhance it when relevant (i.e., Emotion focus) and diminish it when not relevant (i.e., Context focus) (Depue et al., 2007). Given the similarity with the response observed in AMY and IFC and their positive co-variation, it is possible that the involvement of some IFC areas reflects the enhancement of the emotional (re)experiencing during the Emotion focus, for both positive and negative AMs, and reduced engagement for positive AMs along with active inhibition of the emotional information (possibly automatically initiated by the AMY) for negative AMs during the Context focus. Overall, these findings suggest that positive AMs can trigger a strong emotional response only if there is an explicit emphasis on the re-experiencing of emotion during remembering, and that this occurs in relationship with activity in the AMY.

HEMISPHERIC DISSOCIATION IN THE IFC LINKED TO THE EXPERIENCING OF EMOTION AND THE FOCUS OF AM RECOLLECTION

These findings suggest a role of the IFC in the modulation (both enhancement and reduction) of emotional experience. The lateralization of these effects could be interpreted in line with previous evidence linking the left frontal cortex to the retrieval of emotional knowledge during up-regulation of emotional response and the right frontal cortex to inhibitory processes during down-regulation of emotional response (Ochsner et al., 2004; Kim and Hamann, 2007). It should be noted that the positive relationship in the left IFC extends to the anterior ventral insula, which is typically

co-activated with the IFC (Uddin et al., 2013) and is linked to emotion processing (Chang et al., 2012; Kelly et al., 2012; Lindquist et al., 2012), particularly to the awareness of emotional experiences (Craig, 2009; Zaki et al., 2012). Given that in the Emotion AM condition participants were explicitly instructed to focus on emotional details, including the associated sensations and feelings (e.g., butterflies in the stomach, palpitations), the present findings are consistent with a possible contribution of the Anterior Insula together with the IFC to the enhanced emotional experience during Emotion focus, as reflected in the post-retrieval emotional ratings.

Considering altogether the present findings, it could be speculated that the IFC's role in enhancing and inhibiting emotion processing may be linked to its more general involvement according to the relevance of processed information to the current goal (Beer et al., 2006). Specifically, when the emotional information is relevant to the current goal (i.e., retrieval focus on emotional details), it can benefit from enhanced processing through the involvement of IFC, whereas when emotional information is not relevant to the current goal (i.e., retrieval focus on non-emotional contextual details), it can be attenuated or inhibited (Conway and Pleydell-Pearce, 2000; Levine and Edelstein, 2009). Finally, the present brain imaging findings, along with the behavioral findings showing an overall reduction of experienced emotion during the Context focus, could also be linked to the manipulation of attentional deployment, as an emotion regulation strategy, which involves a shift in attention away from the emotional aspects of emotion eliciting events by engaging in a competing task (Gross, 2008), or by changing the focus of the recollected memories, as it is the case in the present study.

In summary, the present findings suggest that the IFC's involvement during the recollection of emotional AMs is susceptible to manipulations of the retrieval focus only in the case of positive AMs, and that this region plays a role in both the enhancement and the inhibition of emotional experience during AM recollection. These findings have direct relevance for therapeutic interventions in affective disorders by pointing to the fact that the increased effectiveness of positive AMs in triggering strong emotional responses, and therefore in alleviating negative mood, occurs only when specific re-experiencing of positive emotions is explicitly emphasized during autobiographical recollection.

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REFERENCES

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016

Aron, A. R., Robbins, T. W., and Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn. Sci.* 8, 170–177. doi:10.1016/j.tics.2004.02.010

Baciu, M. V., Rubin, C., Decorps, M. A., and Segebarth, C. M. (1999). fMRI assessment of hemispheric language dominance using a simple inner speech paradigm. *NMR Biomed.* 12, 293–298. doi:10.1002/(SICI)1099-1492(199908)12:5<293::AID-NBM573>3.3.CO;2-Y

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn. Sci.* 12, 193–200. doi:10.1016/j.tics.2008.02.004

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–2901. doi:10.1016/j.neuropsychologia.2007.06.015

Battig, W. F., and Montague, W. E. (1969). Category norms of verbal items in 56 categories A replication and extension of the connecticut category norms. *J. Exp. Psychol.* 80, 1–46. doi:10.1037/h0027577

Beer, J. S., Knight, R. T., and D'Esposito, M. (2006). Controlling the integration of emotion and cognition: the role of frontal cortex in distinguishing helpful from hurtful emotional information. *Psychol. Sci.* 17, 448–453. doi:10.1111/j.1467-9280.2006.01726.x

Brand, M., and Markowitsch, H. J. (2006). "Memory processes and the orbitofrontal cortex," in *The Orbitofrontal Cortex*, eds D. H. Zald and S. L. Rauch (Oxford: Oxford University Press), 285–306.

Brand, M., and Markowitsch, H. J. (2008). "The role of the prefrontal cortex in episodic memory," in *Handbook of Episodic Memory* (Handbook of behavioral neuroscience, Vol. 18), eds E. Dere, J. P. Huston, and A. Easton (Amsterdam: Elsevier), 317–341.

Brewin, C. R., Reynolds, M., and Tata, P. (1999). Autobiographical memory processes and the course of depression. *J. Abnorm. Psychol.* 108, 511–517. doi:10.1037/0021-843X.108.3.511

Chang, L. J., Yarkoni, T., Khaw, M. W., and Sanfey, A. G. (2012). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb. Cortex* 23, 739–749. doi:10.1093/cercor/bhs065

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–288. doi:10.1037/0033-295X.107.2.261

Conway, M. A., Turk, D. J., Miller, S. L., Logan, J., Nebes, R. D., Meltzer, C. C., et al. (1999). A positron emission tomography (PET) study of autobiographical memory retrieval. *Memory* 7, 679–702. doi:10.1080/096582199387805

Craig, A. D. (2009). How do you feel – now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi:10.1038/nrn2555

Dalgleish, T., Navrady, L., Bird, E., Hill, E., Dunn, B. D., and Golden, A. M. (2013). Method-of-loci as a mnemonic device to facilitate access to self-affirming personal memories for individuals with depression. *Clin. Psychol. Sci.* doi:10.1177/2167702612468111

D'Argembeau, A., and Van der Linden, M. (2008). Remembering pride and shame: self-enhancement and the phenomenology of autobiographical memory. *Memory* 16, 538–547. doi:10.1080/09658210802010463

Daselaar, S. M., Rice, H. J., Greenberg, D. L., Cabeza, R., LaBar, K. S., and Rubin, D. C. (2008). The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. *Cereb. Cortex* 18, 217–229. doi:10.1093/cercor/bhm048

Denkova, E., Chakrabarty, T., Dolcos, S., and Dolcos, F. (2011). Brain imaging investigation of the neural correlates of emotional autobiographical recollection. *J. Vis. Exp.* 54, p. ii:2396. doi:10.3791/2396

Denkova, E., Dolcos, S., and Dolcos, F. (2012). Reliving emotional personal memories: affective biases linked to personality and sex-related differences. *Emotion* 12, 515–528. doi:10.1037/a0026809

Denkova, E., Dolcos, S., and Dolcos, F. (2013). The effect of the retrieval focus and valence on the medial temporal lobe activity during autobiographical recollections. *Front. Behav. Neurosci.* 7:109. doi:10.3389/fnbeh.2013.00109

Depue, B. E., Curran, T., and Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science* 317, 215–219. doi:10.1126/science.1139560

Diener, E., and Seligman, M. E. (2002). Very happy people. *Psychol. Sci.* 13, 81–84. doi:10.1111/1467-9280.00415

Dolcos, F., Diaz-Granados, P., Wang, L., and McCarthy, G. (2008). Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. *Neuropsychologia* 46, 326–335. doi:10.1016/j.neuropsychologia.2007.07.010

Dolcos, F., Iordan, A. D., and Dolcos, S. (2011). Neural correlates of emotion-cognition interactions: a review of evidence from brain imaging investigations. *J. Cogn. Psychol. (Hove)* 23, 669–694. doi:10.1080/20445911.2011.594433

Dolcos, F., Iordan, A. D., Kragel, J., Stokes, J., Campbell, R., McCarthy, G., et al. (2013). Neural correlates of opposing effects of emotional distraction on working

memory and episodic memory: an event-related FMRI investigation. *Front. Psychol.* 4:293. doi:10.3389/fpsyg.2013.00293

Dolcos, F., Kragel, P., Wang, L., and McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *Neuroreport* 17, 1591–1594. doi:10.1097/01.wnr.0000236860.24081.be

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *Neuroimage* 23, 64–74. doi:10.1016/j.neuroimage.2004.05.015

Fletcher, P. C., and Henson, R. N. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124(Pt 5), 849–881. doi:10.1093/brain/124.5.849

Fredrickson, B. L. (2004). The broaden-and-build theory of positive emotions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 359, 1367–1378. doi:10.1098/rstb.2004.1512

Fuster, J. M. (2002). Frontal lobe and cognitive development. *J. Neurocytol.* 31, 373–385. doi:10.1023/A:1024190429920

Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., and Labar, K. S. (2005). Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia* 43, 659–674. doi:10.1016/j.neuropsychologia.2004.09.002

Grindrod, C. M., Bilenko, N. Y., Myers, E. B., and Blumstein, S. E. (2008). The role of the left inferior frontal gyrus in implicit semantic competition and selection: an event-related fMRI study. *Brain Res.* 1229, 167–178. doi:10.1016/j.brainres.2008.07.017

Gross, J. J. (2008). "Emotion regulation," in *Handbook of Emotions*, eds M. Lewis, J. M. Haviland-Jones, and L. F. Barrett (New York, NY: Guilford), 497–512.

Hagoort, P. (2005). On Broca, brain, and binding: a new framework. *Trends Cogn. Sci.* 9, 416–423. doi:10.1016/j.tics.2005.07.004

Hooker, C. I., and Knight, R. T. (2006). "Role of the orbitofrontal cortex in the inhibition of emotion," in *The Orbitofrontal Cortex*, eds D. H. Zald and S. L. Rauch (New York: Oxford University Press), 307–324.

Iordan, A., Dolcos, S., and Dolcos, F. (2013). Neural signatures of the response to emotional distraction: a review of evidence from brain imaging investigations. *Front. Hum. Neurosci* 7:200. doi:10.3389/fnhum.2013.00200

Joormann, J., Siemer, M., and Gotlib, I. H. (2007). Mood regulation in depression: differential effects of distraction and recall of happy memories on sad mood. *J. Abnorm. Psychol.* 116, 484–490. doi:10.1037/0021-843X.116.3.484

Kelly, C., Toro, R., Di Martino, A., Cox, C. L., Bellec, P., Castellanos, F. X., et al. (2012). A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage* 61, 1129–1142. doi:10.1016/j.neuroimage.2012.03.021

Kim, S. H., and Hamann, S. (2007). Neural correlates of positive and negative emotion regulation. *J. Cogn. Neurosci.* 19, 776–798. doi:10.1162/jocn.2007.19.5.776

Levine, L. J., and Edelstein, R. S. (2009). Emotion and memory narrowing: a review and goal-relevance approach. *Cogn. Emot.* 23, 833–875. doi:10.1080/02699930902738863

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., and Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 35, 121–143. doi:10.1017/S0140525X11000446

Markowitsch, H. J. (1995). Which brain regions are critically involved in the retrieval of old episodic memory? *Brain Res. Brain Res. Rev.* 21, 117–127. doi:10.1016/0165-0173(95)00007-0

Markowitsch, H. J., Thiel, A., Reinkemeier, M., Kessler, J., Koyuncu, A., and Heiss, W. D. (2000). Right amygdalar and temporofrontal activation during autobiographic, but not during fictitious memory retrieval. *Behav. Neurol.* 12, 181–190.

Markowitsch, H. J., Vandekerckhove, M. M., Lanfermann, H., and Russ, M. O. (2003). Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. *Cortex* 39, 643–665. doi:10.1016/S0010-9452(08)70858-X

McGuire, P. K., Silbersweig, D. A., Murray, R. M., David, A. S., Frackowiak, R. S., and Frith, C. D. (1996). Functional anatomy of inner speech and auditory verbal imagery. *Psychol. Med.* 26, 29–38. doi:10.1017/S0033291700033699

Morin, A., and Michaud, J. (2007). Self-awareness and the left inferior frontal gyrus: inner speech use during self-related processing. *Brain Res. Bull.* 74, 387–396. doi:10.1016/j.brainresbull.2007.06.013

Moss, H. E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., et al. (2005). Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. *Cereb. Cortex* 15, 1723–1735. doi:10.1093/cercor/bhi049

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23, 483–499. doi:10.1016/j.neuroimage.2004.06.030

Ochsner, K. N., Silvers, J. A., and Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann. N. Y. Acad. Sci.* 1251, E1–E24. doi:10.1111/j.1749-6632.2012.06751.x

Petrides, M., and Pandya, D. N. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Eur. J. Neurosci.* 16, 291–310. doi:10.1046/j.1460-9568.2001.02090.x

Piolino, P., Giffard-Quillon, G., Desgranges, B., Chetelat, G., Baron, J. C., and Eustache, F. (2004). Re-experiencing old memories via hippocampus: a PET study of autobiographical memory. *Neuroimage* 22, 1371–1383. doi:10.1016/j.neuroimage.2004.02.025

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10, 15–35. doi:10.1006/nimg.1999.0441

Rubin, D. C., Berntsen, D., and Bohni, M. K. (2008). A memory-based model of posttraumatic stress disorder: evaluating basic assumptions underlying the PTSD diagnosis. *Psychol. Rev.* 115, 985–1011. doi:10.1037/a0013397

Salas, C. E., Radovic, D., and Turnbull, O. H. (2012). Inside-out: comparing internally generated and externally generated basic emotions. *Emotion* 12, 568–578. doi:10.1037/a0025811

Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208. doi:10.1016/j.neuropsychologia.2006.05.023

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc. Natl. Acad. Sci. U.S.A.* 94, 14792–14797. doi:10.1073/pnas.94.26.14792

Thompson-Schill, S. L., D'Esposito, M., and Kan, I. P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron* 23, 513–522. doi:10.1016/S0896-6273(00)80804-1

Uddin, L. Q., Kinnison, J., Pessoa, L., and Anderson, M. L. (2013). Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *J. Cogn. Neurosci.* 26, 16–27. doi:10.1162/jocn_a_00462

Wager, T. D., Barrett, L. F., Bliss-Moreau, E., Lindquist, K., Duncan, S., Kober, H., et al. (2008). "The neuroimaging of emotion," in *Handbook of Emotion*, eds M. Lewis, J. M. Haviland-Jones, and L. F. Barrett (New York: Guilford), 249–271.

Werner-Seidler, A., and Moulds, M. L. (2011). Autobiographical memory characteristics in depression vulnerability: formerly depressed individuals recall less vivid positive memories. *Cogn. Emot.* 25, 1087–1103. doi:10.1080/02699931.2010.531007

Werner-Seidler, A., and Moulds, M. L. (2012). Mood repair and processing mode in depression. *Emotion* 12, 470–478. doi:10.1037/a0025984

Young, K. D., Bellgowan, P. S., Bodurka, J., and Drevets, W. C. (2013). Functional neuroimaging of sex differences in autobiographical memory recall. *Hum. Brain Mapp.* 34, 3320–3332. doi:10.1002/hbm.22144

Zaki, J., Davis, J. I., and Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. *Neuroimage* 62, 493–499. doi:10.1016/j.neuroimage.2012.05.012

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The effect of retrieval focus and emotional valence on the medial temporal lobe activity during autobiographical recollection

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Laboratory-based episodic memory studies, using micro-events (pictures/words), point to a role of the amygdala (AMY), an emotion-based region, in the encoding and retrieval of emotionally valenced memories. However, autobiographical memory (AM) studies, using real-life personal events, do not conclusively support AMY's involvement in AM recollection. This could be due to differences in instructions across the AM studies – i.e., whether emotional aspects were explicitly emphasized or not. The present study investigated the effect of retrieval focus on activity in emotion (AMY) and memory (hippocampus – HC) based regions of the medial temporal lobe in 17 subjects, who remembered emotional AMs while event-related fMRI data were recorded. The retrieval focus was manipulated by instructions to focus either on emotional (*Emotion* condition) or on other contextual (*Context* condition) details of the recollected AMs. The effect of retrieval focus according to the valence of AMs was also investigated by involving an equal proportion of positive and negative AMs. There were four main findings, showing both similarities and differences in retrieving positive and negative AMs. Regarding similarities, (1) focusing on Emotion was associated with increased scores of subjective re-experience of emotion and increased activity in the left AMY, for both positive and negative AMs, compared to focusing on Context; (2) the subjective emotional ratings were also positively correlated with bilateral AMY activity for both positive and negative AMs. Regarding differences, (3) focusing on Emotion was associated with increased activity for positive but not for negative AMs in the right AMY, and with (4) opposing patterns of activity linked to the valence of AMs in the left HC – i.e., increased activity for positive and decreased activity for negative AMs. These findings shed light on the role of AMY and HC in emotional AM recollection, linked to the retrieval focus and the valence of memories.

Keywords: personal memories, retrieval goal, fMRI, MTL, valence

INTRODUCTION

Remembering emotional autobiographical memories (AMs) is an integral part of everyday life that may influence personal well-being and psychological health. Thinking about emotional personal experiences can be used to re-experience positive affect (Bluck and Alea, 2009a) or to reverse negative mood (Josephson et al., 1996; Joormann et al., 2007). However, empirical research has mainly focused on the consequences of reflecting on negative experiences, and has produced contradictory findings. Reflecting on negative events has been found either to reduce the intensity of those experiences (Pennebaker and Graybeal, 2001; Wilson and Gilbert, 2008) or to increase negative affect (Mor and Winquist, 2002; Nolen-Hoeksema et al., 2008; Smith and Alloy, 2009), which may lead to depression. These inconsistent findings might be due, in part, to the type of focus people adopt when recollecting personal experiences, such as focusing on the emotional aspects or on other non-emotional details of the experience (e.g., when and where personal events occurred).

Neuroimaging evidence from "emotional" AM studies[1] (Svoboda et al., 2006) has associated the retrieval of emotional AMs with activity in emotion (amygdala – AMY) and memory (hippocampus – HC) related medial temporal lobe (MTL) regions (Markowitsch et al., 2000; Piefke et al., 2003). Moreover, activity in the AMY and HC was associated with the emotional intensity of memories (e.g., Botzung et al., 2010). This evidence is consistent with findings from laboratory-based episodic memory studies, which have demonstrated greater engagement of both emotion

[1] Referring to AM studies specifically eliciting the recall of emotional memories, as opposed to "standard" AM studies, referring to studies without explicit instructions to retrieve emotional aspects of memories (see meta-analysis by Svoboda et al., 2006).

and memory MTL systems during encoding (Dolcos et al., 2004; Kensinger and Corkin, 2004; Kensinger and Schacter, 2006; Sergerie et al., 2006), consolidation (Ritchey et al., 2008), and retrieval (Hamann et al., 1999; Dolcos et al., 2005; Sergerie et al., 2006) of emotional items (reviewed in Dolcos et al., 2012). However, the majority of the "standard" AM studies have not identified AMY involvement during retrieval of personal events or its modulation by emotional intensity (Maguire and Frith, 2003; Addis et al., 2004; but see Daselaar et al., 2008).

The inconsistencies in the AMY engagement during retrieval of AMs could be due to several factors (Greenberg et al., 2005; Denkova et al., 2006; Markowitsch and Staniloiu, 2011). First, it is possible that differences in image acquisition parameters and in statistical analyses (whole-brain vs. ROI analysis) could, at least partially, account for the inconsistencies in AMY activation across these studies (Greenberg et al., 2005). Second, AMY may be involved only in recollections that are sufficiently vivid and strong to elicit a re-experience of the associated emotion (Ochsner and Schacter, 2000). Third, because of the complexity and multifaceted nature of autobiographical events, it is possible that more elaborative processing and cognitive resources needed for their constructive retrieval may attenuate AMY's involvement during the "standard" AM studies (Denkova et al., 2006; Dolcos et al., 2012). Finally, given that the "standard" AM studies commonly ask participants to retrieve a specific event without a clear and explicit focus on emotional aspects of recollections (Svoboda et al., 2006), and that the episodic laboratory-based memory studies suggest a goal-modulated involvement of the AMY (Smith et al., 2006), it is reasonable to infer that the retrieval instructions given to the participants may influence the AMY engagement during the recollection of personal events. However, this possibility has never been tested and clarified in the AM neuroimaging literature.

The main goal of the present study was to investigate the effect of manipulating the retrieval focus (on emotional vs. on non-emotional, contextual, aspects) on the involvement of emotion (AMY) and memory (HC) related MTL regions during remembering of emotional AMs. In addition, the role of *valence* (positive or negative), which is an important and understudied aspect of AMs, was also investigated. Available evidence suggests that positive and negative AMs may be governed by different mechanisms and lead to different outcomes. Specifically, positive or negative affective biases in AM recollection are closely linked to personal well-being or impaired mental health, respectively. For instance, a positive memory bias in recollections of past personal events and in simulations of future personal events is reported in normal population and healthy aging (Bluck and Alea, 2009b; Denkova et al., 2012; Finnbogadottir and Berntsen, 2012; Szpunar et al., 2012; Rasmussen and Berntsen, 2013), while a negative memory bias is reported in people with/or susceptible to affective disorders, such as depression and post-traumatic stress disorder (PTSD) (MacLeod and Byrne, 1996; Brewin et al., 1999; Nolen-Hoeksema et al., 2008). The valence of AMs can also modulate brain activity. For example, across the few AMs neuroimaging studies considering the valence of memories, recollection of positive personal events has been shown to engage MTL regions linked to greater re-experience of positive events, and orbito-frontal regions, which are involved in the representation of rewarding experiences; on the other hand, recollection of negative AMs engages lateral temporal regions, linked to the processing of negative emotions (Markowitsch et al., 2003; Piefke et al., 2003, but see Vandekerckhove et al., 2005, which failed to observe such an effect).

To investigate these issues, fMRI data were recorded while participants focused either on emotional (*Emotion* condition) or on other contextual (*Context* condition) details during elaboration of recollected positive and negative AMs. In the Emotion condition, participants were instructed to remember past events by focusing on the emotional aspects of their recollections, whereas in the Context condition participants were instructed to remember past events by focusing on other, non-emotional, contextual details (e.g., details about the time and place of personal events). Based on the extant evidence, we made the following predictions. Concerning the behavioral results, we predicted increased emotional ratings for both positive and negative AMs when focusing on emotional details of the recollected AMs. Concerning the fMRI results, we predicted both similar and dissociable effects in the MTL regions, linked to the retrieval focus and the emotional valence of the AMs. Specifically, we expected overall similar greater engagement of MTL activity during AMs recollection in the *Emotion* condition than in the *Context* condition, for both positive and negative memories. We also expected a link between increased emotional ratings and AMY activity in the *Emotion* condition. Finally, based on evidence that positive and negative AMs may be governed by different mechanisms, we also expected a dissociable engagement of MTL regions according to the valence of memories, possibly with positive memories leading to greater MTL engagement, particularly in the *Emotion* condition.

MATERIALS AND METHODS

PARTICIPANTS

Eighteen right-handed native English speaking young adults with no history of neurological, psychological, or psychiatric illness participated in this study (six men; age range 18–46, mean = 26 years, SD = 7.02). One subject dropped out the study after the first run of the fMRI session, hence, data from 17 subjects (six men, mean age = 26.06 years; SD = 7.20) were analyzed. The experimental protocol was approved by the Institutional Health Research Ethics Board, and all participants provided written informed consent and received payment for their participation.

COLLECTION AND SELECTION OF EMOTIONAL AUTOBIOGRAPHICAL MEMORIES

Personal memories were elicited from each participant during an interview performed ∼5 weeks prior to the fMRI session, similar to other AM neuroimaging studies (Markowitsch et al., 2000; Maguire and Frith, 2003; Piefke et al., 2003; Addis et al., 2004; Botzung et al., 2008). This procedure allows increased control over the properties of the memories to be used in different trial types, as compared to involving AM retrieval directly in the scanning session (Maguire, 2001; Cabeza and St Jacques, 2007; St Jacques, 2012). In addition, it attenuates the disadvantage of reactivation by interposing sufficient time between the pre-scan interview and the subsequent scanning session (Maguire and Mummery, 1999). We used an autobiographical memory questionnaire (AMQ) specifically constructed to target the assessment of emotional personal

episodes and their recollective properties (Denkova et al., 2012). The AMQ comprised a list of 115 verbal cues for distinct life events (e.g., "the birth of a family member," "being hospitalized"), resulted from a combination and extension of lists employed by other authors (Levine et al., 2002; Markowitsch et al., 2003; Sharot et al., 2007). For each cue, participants were asked to remember a unique episode from their life, that occurred in a specific place and time (e.g., one instance when s/he played in a specific basketball game), rather than remembering general or repeated events (e.g., playing basketball in high school). Importantly, the memories had to be accompanied by the recollection of being personally involved, rather than hearing about them from others. Upon recollection, participants were asked to provide a brief description of the memory, which was then used as a personalized memory cue during the fMRI scanning; at the time of collecting the AMs, participants were naïve to the specific purpose of the pre-scanning interview. To assess phenomenological characteristics of each event, participants dated the memory and rated it on several Likert scales, similar to those used in other AM studies (Addis et al., 2004; Greenberg et al., 2005), as follows: Emotional Valence (using a 7-point scale: −3 = very negative, 0 = neutral, and +3 = very positive), Emotional Intensity, Personal Significance, Vividness (i.e., the amount of visuo-perceptual details), the amount of Contextual Details, and the Frequency of Retrieval (all of the latter used a 7-point scale: 1 = not at all, 7 = extremely).

For each participant, we selected the 40 most emotional memories (20 positive and 20 negative), based on the ratings provided on the AMQ (i.e., rated 2 or 3 and −2 or −3, respectively). Half of the selected memories, with an equal proportion of positive and negative AMs, were assigned to an *Emotion* Retrieval Focus AM condition (10 positive and 10 negative), and the other half of AMs were assigned to a *Context* Retrieval Focus AM condition (10 positive and 10 negative). This resulted in four AM event types: Emotion Focus Positive, Emotion Focus Negative, Context Focus Positive, and Context Focus Negative Memories. To ensure that any differences between the two retrieval foci/goals during the fMRI session would not be due to initial differences in the properties of the memories assigned to the Emotion and Context conditions, the positive and negative memories of the two conditions were matched as closely as possible in terms of phenomenological properties (see **Table 1**). The descriptions provided by the participants were used to create memory cues specific for each participant. If necessary, the descriptions were slightly adapted to be matched as closely as possible in terms of length and grammatical complexity. Four other memories were also selected and used in practice trials before the fMRI session.

fMRI TASKS

The fMRI session comprised two AM tasks, according to retrieval focus (*Emotion* and *Context*), and a semantic memory (SM) control task. Given the goal of the present investigation, in each AM task, half of the memories were positive and the other half were negative. Just before performing the fMRI tasks, participants were given detailed instructions and examples for the tasks they had to perform in the scanner. In addition, participants performed practice trials in order to familiarize themselves with the tasks and to ensure that they understood the instructions.

The autobiographical memory tasks

Participants were asked to retrieve the memories associated with each personalized memory cue by either focusing on emotional (*Emotion* condition) or focusing on other contextual (*Context* condition) aspects of their positive and negative memories. For the *Emotion* condition, participants were instructed to remember the specific event and focus on the emotional aspects of their memories, including associated sensations and feelings that they may have triggered (e.g., butterflies in the stomach, palpitations). For the *Context* condition, participants were instructed to remember the specific event and focus on other, non-emotional, contextual aspects of their memories, by retrieving as many contextual details as possible (e.g., about where and when the event occurred, who else was involved, etc.). Each memory cue was preceded by an instruction cue, as follows: "Remember Emotion," for the Emotion condition, and "Remember Context," for the Context condition, respectively. Once the memory cue appeared on the screen, participants had to indicate by a button press that they recognized the cue as belonging to them, and then continued remembering details of the event until cued to rate the recollected memory. Each recollection was rated on three five-point Likert scales including Emotional Intensity, Vividness, and Reliving (1 = very low; 5 = very high). The participants were instructed to make quick (spontaneous) and accurate responses and to use the whole scale.

The semantic memory control task

In line with other AM functional neuroimaging studies (Greenberg et al., 2005; Young et al., 2012), we used a control

Table 1 | Phenomenological properties of the selected autobiographical memories.

	Negative		*t* test, *p*	Positive		*t* test, *p*
	Emotion	Context		Emotion	Context	
Emotional intensity	5.68 (0.51)	5.70 (0.52)	0.60	5.25 (0.83)	5.29 (0.82)	0.20
Vividness	5.19 (0.80)	5.15 (0.67)	0.47	5.54 (0.61)	5.49 (0.73)	0.52
Contextual details	4.94 (1.06)	4.92 (1.12)	0.72	5.38 (1.17)	5.30 (1.25)	0.32
Personal significance	4.42 (1.02)	4.32 (1.08)	0.09	4.69 (1.01)	4.73 (0.93)	0.61
Frequency of rehearsal	3.33 (1.04)	3.32 (0.96)	0.87	3.64 (0.96)	3.54 (0.95)	0.20

Standard deviations are given in parentheses. There were no significant differences between memories assigned to the Emotion condition and those assigned to the Context condition.

condition involving SM retrieval. Specifically, the SM task involved generation of exemplars from 20 different semantic categories (e.g., musical instruments, sports, vegetables) (Battig and Montague, 1969), which like the AM retrieval involves search in memory and extended retrieval time. The participants were presented with a semantic category name cue (e.g., fruits, vegetables) and instructed to recall as many exemplars as possible for each category. Each semantic category cue was preceded by an instruction cue ("Generate Examples"). Once the category cue appeared on the screen, participants had to indicate by a button press that they started recalling exemplars from the category, and then they continued recalling until cued again for memory ratings. To be consistent with AM conditions, each exemplar generation was rated on three five-point Likert scales appropriate for SM generation – i.e., Vividness, Difficulty of the task (1 = very low; 5 = very high), and approximate Number of the recalled items (1 = 1 to 3 items; 5 = 15 or more items).

fMRI DESIGN AND PROCEDURE

The AM conditions and the SM control condition had the same general structure (see **Figure 1**). Each trial began with an instruction screen for 2 s, immediately followed by a memory cue for 4 s. After the cue offset, a fixation screen was presented for 10 s during which participants elaborated their personal memories or generated exemplars. The end of the retrieval period was marked by the presentation of an instructions screen for upcoming ratings, for 1.5 s. Then, each of the three ratings was presented for 2.5 s and in a counterbalanced order across trials. The ratings were followed by an inter-trial interval of variable duration (2–9 s, average = 6 s), before the beginning of the next trial.

The scanning session was divided into two parts of four runs. Each run started with a 6-s fixation, to allow stabilization of the fMRI signal, and comprised five trials from each condition (Emotion, Context, and Semantic). To avoid induction of longer-lasting effects, the trials within each run were pseudo-randomized, so that no more than two consecutive trials of the same type were presented. To prevent possible biases resulted from using the same run order, participants were assigned different run orders. Similar to other AM neuroimaging studies (Greenberg et al., 2005), in order to increase statistical power, the four runs from the first part were immediately repeated in the second part of the scanning session, and the order of the runs was counterbalanced across participants. Stimuli were projected on a screen directly behind the subjects' heads within the scanner, which they viewed through a mirror.

All stimuli appeared in white letters against a black background created in Adobe Photoshop. The CIGAL software (http://www.nitrc.org/projects/cigal/) was used for stimulus presentation and collection of behavioral responses during the fMRI session. All responses were made on a four-button MRI-compatible response box placed under the subject's right hand; the fifth rating was indicated by the participants with a double click on button #1.

MRI DATA COLLECTION

MRI data were recorded using a 1.5-T Siemens Sonata scanner. The anatomical images were 3D MPRAGE anatomical series (repetition time [TR] = 1600 ms, echo time [TE] = 3.82 ms, field of view [FOV] = 256 mm × 256 mm, number of slices = 112, voxel size = 1 mm × 1 mm × 1 mm). The functional images consisted of series of images acquired axially using an echoplanar sequence (TR = 2000 ms, TE = 40 ms, FOV = 256 mm × 256 mm, number of slices = 28, voxel size = 4 mm × 4 mm × 4 mm).

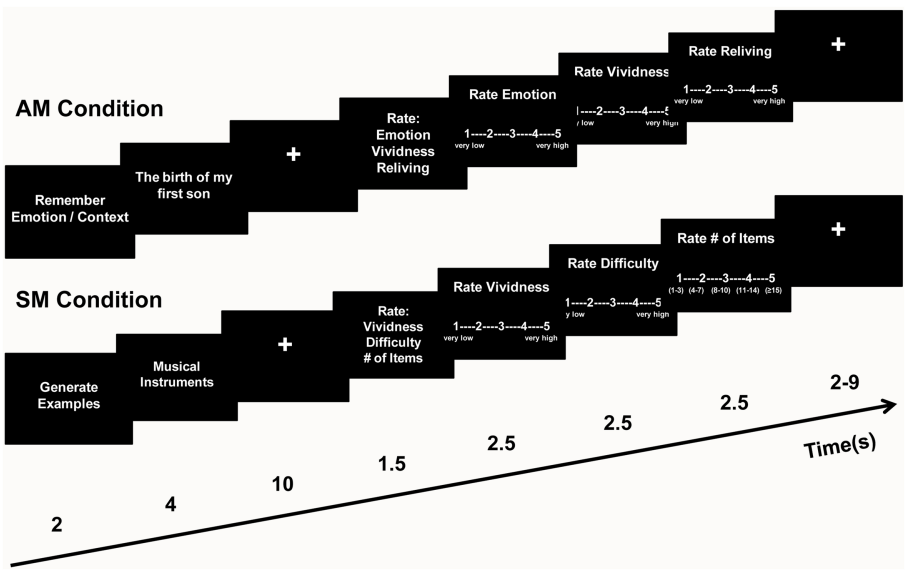


FIGURE 1 | Diagram of the task. During the Autobiographical Memory (AM) conditions, participants remembered highly emotional personal memories by focusing either on emotional (Emotion) or on other contextual (Context) aspects of their recollections, and then rated each AM for Emotional Intensity, Vividness, and Reliving on five-point scales. During the control Semantic Memory (SM) condition, participants generated as many exemplars as possible from a given semantic category, and then rated each of them for Vividness, Difficulty, and Number of Items on five-point scales.

BEHAVIORAL DATA ANALYSIS

To investigate the effect of retrieval focus on the qualities of the negative and positive remembered memories, we performed repeated-measures ANOVA with three factors: Focus (Emotion, Context), Valence (Negative, Positive), and Ratings (Emotional Intensity, Reliving, Vividness).

fMRI DATA ANALYSIS

Statistical analyses, performed with SPM2 (Statistical Parametric Mapping), were preceded by the following pre-processing steps: Quality Assurance, TR Alignment, Motion Correction, Coregistration, Normalization, and Smoothing (8 mm full-width half maximum isotropic Kernel). At the individual level, each event was modeled by the canonical hemodynamic response function (*hrf*) and its temporal derivate. Movement parameters calculated during the realignment were included as parameters of no interest to control for movement artifacts. According to previous AM neuroimaging studies (Addis et al., 2007), to allow for reading the cue, the *hrf* was time-locked to 2 s (1TR) following the onset of the memory cues, in the Emotion and Context AM conditions, and 1 s (0.5TR) after the onset of the category cue, in the SM condition. Consistent with these, investigation of the RT data showed that the recognition of the AM cues occurred at an average RT of 1.67 s (±0.44), and the beginning of exemplar generation in the SM condition occurred at an average RT of 1.03 s (±0.40). For the fMRI analysis according to focus and valence, we selected randomly only 10 SM events to match the numbers of each of the four AM event types. Individual contrasts were computed directly between the different AM event types (e.g., Emotion Positive vs. Context Positive, Emotion Negative vs. Context Negative). These individual contrasts were then entered into group-level *t* tests, to perform random-effects analyses. The SPM analyses were complemented by analyses performed with in-house MATLAB tools (Dolcos and McCarthy, 2006; Denkova et al., 2010), which allowed extraction of the fMRI signal and examination of the time course of activity related to different conditions, across the whole length of the trials.

To investigate the effects of retrieval focus on positive memories in MTL regions, we compared positive AMs with Emotion focus and positive AMs with Context focus (Emotion Positive > Context Positive and Context Positive > Emotion Positive). Similarly, to investigate the effects of retrieval focus on negative memories, we performed the following comparisons: Emotion Negative > Context Negative and Context Negative > Emotion Negative. Additionally, to also investigate the effect of valence within each retrieval focus, we compared positive and negative AMs with Emotion focus (Emotion Positive > Emotion Negative and Emotion Negative > Emotion Positive) and positive and negative AMs with Context focus (Context Positive > Context Negative and Context Negative > Context Positive).

The common effects of the retrieval focus on both positive and negative memories were investigated through conjunction analyses [e.g. (Emotion Positive vs. Context Positive) ∩ (Emotion Negative vs. Context Negative)]. The dissociating effects of the retrieval focus and valence were investigated through interaction analyses using paired *t* tests [e.g., (Emotion Positive vs. Context Positive) vs. (Emotion Negative vs. Context Negative)], whose outputs were inclusively masked with the corresponding direct effect (e.g., Emotion Positive vs. Context Positive) to ensure that the interaction difference is due to an existing increased difference in the comparisons/contrasts of interest. Finally, to investigate whether differential activity in the MTL according to the focus of retrieval is linked to differences in the subjective feeling of emotion, linear regression analyses were performed between difference scores in self-reported emotion ratings (Emotion ratings minus Context ratings) and MTL activity for Emotion > Context contrasts, for positive and negative AMs, respectively.

As the main goal of the study was to investigate the effects of retrieval focus and valence of AMs on emotion- and memory-related MTL regions, we used anatomical masks of the AMY and HC, based on the Wake Forest University Pick Atlas toolbox. Overall, for all ROI analyses in the AMY and HC, identified as regions of *a priori* interest, we used a statistical threshold of $p < 0.05$ and an extent threshold of five contiguous voxels. For completeness, we also report results of whole-brain analyses for regions outside of the MTL. For these analyses, an intensity threshold of $p < 0.001$ was used for the specific direct contrasts and a threshold of $p < 0.005$ was used for the interactions; the extent threshold was of 10 contiguous voxels.

RESULTS

BEHAVIORAL RESULTS

Increased re-experiencing of emotion for both positive and negative AMs in the Emotion condition

Repeated-measures ANOVA revealed a main effect of focus [$F_{(1,16)} = 6.33$, $p = 0.02$], indicating higher ratings for the memories retrieved with the Emotion focus. This effect was qualified by a focus x ratings interaction [$F_{(1,16)} = 4.12$, $p = 0.03$], driven by an increase only for the emotional intensity ratings of AMs retrieved with an emotional focus (Emotion condition); no significant increase was observed in the Reliving and Vividness ratings. The increase was significant for both positive (3.21 vs. 3.03, $p = 0.02$) and negative (3.38 vs. 3.07, $p = 0.003$) AMs (see **Figure 2**), thus

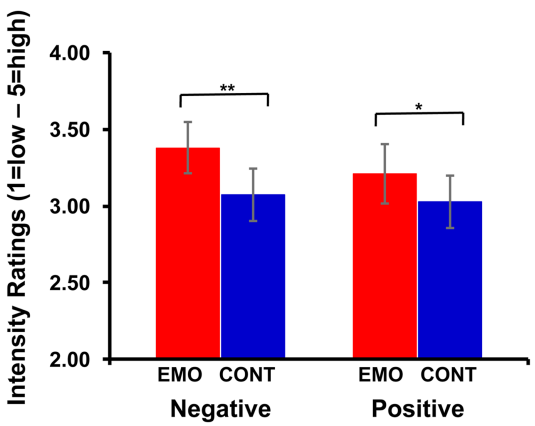


FIGURE 2 | Increased subjective re-experiencing of emotion during Emotion focus retrieval. Self-reported ratings for emotional intensity were higher in the Emotion (EMO) than in the Context (CONT) condition, for both negative (**$p < 0.005$) and positive (*$p < 0.05$) autobiographical memories.

precluding a significant focus x valence x ratings interaction [$F_{(1, 16)} = 1.30$, $p = 0.29$]. Overall, the ratings assessed immediately after recollecting AMs during the scanning sessions showed that the manipulation of the retrieval focus (Emotion vs. Context) dissociated the subjective re-experience of emotion for both positive and negative memories, without affecting significantly the subjectively reported ratings for Reliving and Vividness.

fMRI RESULTS

The present fMRI results revealed both common and dissociable effects of retrieval focus (Emotion vs. Context), linked to the valence of AMs, in emotion (AMY) and memory (HC) related MTL regions.

COMMON EFFECTS OF RETRIEVAL FOCUS ON POSITIVE AND NEGATIVE AM RETRIEVAL IN AMY

Increased activity in left AMY for both positive and negative memories in the Emotion condition

Manipulation of the retrieval focus was associated with increased activity in the left AMY for both positive and negative memories, in the Emotion compared to the Context condition (Emotion > Context) (see **Figure 3** and **Table 2**). Common engagement of this left AMY area during retrieval of both positive and negative AMs was revealed by the following conjunction analysis: [(Emotion Positive > Context Positive) ∩ (Emotion Negative > Context Negative)].

AMY activity linked to subjective re-experiencing of emotion for both positive and negative memories

The difference in AMY activity between Emotion and Context (Emotion > Context) was positively correlated with the difference in emotional intensity ratings between Emotion and Context (intensity ratings in Emotion condition minus intensity ratings in Context condition) (see **Figure 4**). This effect was observed in both left and right AMY and for both positive and negative AMs. For negative memories, the AMY areas showing the correlation with the ratings also overlapped with the area showing greater activity in the Emotion than in the Context condition, in the left ($x = -28$, $y = -1$, $z = -10$; $R = 0.72$, $p = 0.001$), but not in the right ($x = 24$, $y = -1$, $z = -13$; $R = 0.53$, $p = 0.03$) hemisphere. For positive memories, the areas of left and right AMY showing the correlations with emotional ratings ($x = -28$, $y = 7$, $z = -17$; $R = 0.62$, $p = 0.004$, and $x = 24$, $y = 7$, $z = -21$; $R = 0.62$, $p = 0.004$, respectively) showed only very little overlaps with the areas showing increased activity for Emotion compared to the Context condition.

DISSOCIABLE EFFECTS OF RETRIEVAL FOCUS ON POSITIVE AND NEGATIVE AM RETRIEVAL IN AMY AND HC

Increased right AMY activity for positive but not for negative memories in the Emotion condition

Focusing on Emotion compared to Context led to a dissociable pattern of activity in the right AMY for positive and negative AMs (see **Figure 3** and **Table 2**). Specifically, retrieval of positive memories was associated with greater activity in the Emotion than in the Context condition (Emotion Positive > Context Positive), while retrieval of negative memories produced similar effects in the Emotion and Context conditions (Emotion Negative = Context Negative). These effects were confirmed by a repeated-measures ANOVA, performed on the extracted signal, which revealed a significant valence x focus interaction [$F_{(1, 16)} = 6.84$, $p = 0.02$].

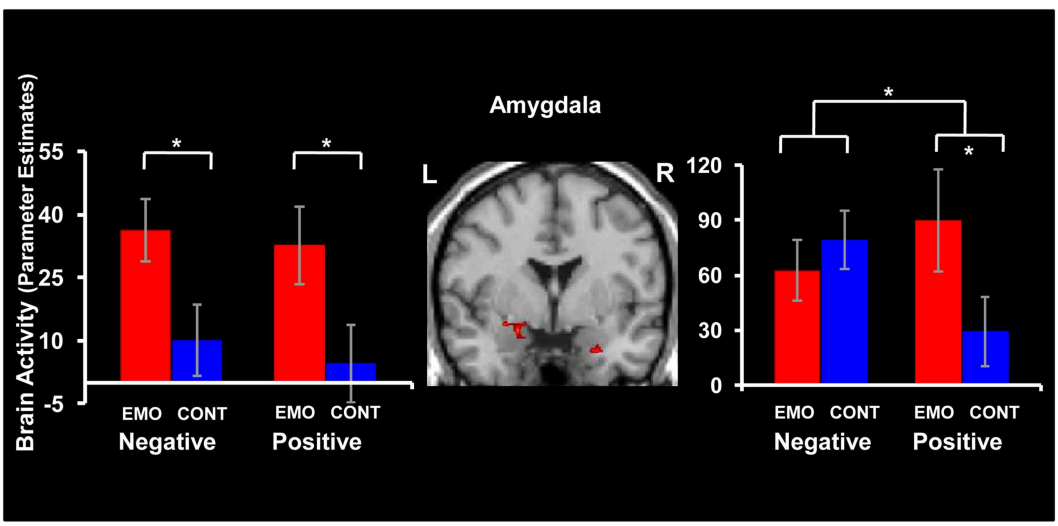


FIGURE 3 | Common and dissociable effects of retrieval focus in the amygdala (AMY), for positive and negative memories. Focusing on Emotion (EMO) compared to focusing on Context (CONT) led to similar increases of activity in the left AMY (left panel) for both positive and negative memories; dissociable patterns of activity linked to valence were observed in the right AMY (right panel). The conjunction and interaction maps for the left and right AMY, respectively, are superimposed on a high resolution brain image displayed in a coronal view. The bar graphs represent the contrasts estimates extracted from representative voxels in the left and right AMY, respectively. The error bars correspond to the standard errors of the means. L = Left, R = Right.

Table 2 | Activations in MTL ROIs linked to the retrieval focus and emotional valence of memories.

MTL regions	Side	Talairach coordinates			*T* score	Cluster size
		x	*y*	*Z*		
A. DIRECT CONTRASTS						
Emotion Negative vs. Context Negative						
Amygdala	L	−20	−4	−10	2.76	13
	L	−32	−1	−10	2.43	
Emotion Positive vs. Context Positive						
Amygdala	L	−32	−1	−10	3.56	32
	R	20	3	−24	3.57	35
Hippocampus	L	−32	−16	−16	3.99	67
	R	32	−27	−5	3.24	52
Context Negative vs. Emotion Negative						
Hippocampus	L	−32	−39	−1	3.56	8
	L	−40	−16	−20	2.32	8
Emotion Positive vs. Emotion Negative						
Hippocampus	L	−36	−24	−9	3.39	21
Context Negative vs. Context Positive						
Amygdala	L	−32	−8	−13	3.59	5
	R	24	−1	−20	3.33	35
Hippocampus	L	−32	−12	−9	4.33	67
	R	32	−12	−13	4.47	59
B. CONJUNCTION						
(Emotion Negative vs. Context Negative) ∩ (Emotion Positive vs. Context Positive)						
Amygdala	L	−32	−1	−10	3.56	12
	L	−24	−1	−13	2.79	
C. INTERACTIONS						
(Emotion Positive vs. Context Positive) vs. (Emotion Negative vs. Context Negative)						
Amygdala	R	24	3	−24	2.66	11
Hippocampus	L	−32	−16	−16	5.06	41
Hippocampus	R	32	−31	−5	2.97	24
(Context Negative vs. Emotion Negative) vs. (Context Positive vs. Emotion Positive)						
Hippocampus	L	−36	−16	−16	3.60	7
	L	−32	−27	−5	2.70	8
(Emotion Positive vs. Emotion Negative) vs. (Context Positive vs. Context Negative)						
Hippocampus	L	−32	−16	−16	5.06	19
(Context Negative vs. Context Positive) vs. (Emotion Negative vs. Emotion Positive)						
Amygdala	R	24	−1	−23	2.61	8
Hippocampus	L	−32	−16	−16	5.06	46
Hippocampus	R	32	−32	−9	3.20	32

Significant activations resulting from direct contrasts, conjunctions, and interactions analyses in a priori targeted MTL ROIs (AMY and HC) are reported. An intensity threshold of $p < 0.05$ and an extent threshold of 5 contiguous voxels were used for all ROI analyses. For the conjunction analyses, a threshold of $p < 0.05$ was used in each of the contributing contrast, and for the interaction analyses the interaction contrast was inclusively masked with the corresponding direct contrast set up at $p < 0.05$ (see Materials and Methods for details). MTL = Medial Temporal Lobe; L = left, R = right.

This interaction was driven by a significant increase in the Emotion condition compared to the Context condition for positive ($p = 0.01$) but not for negative ($p = 0.44$) AMs.

Opposing patterns of activity in the left hippocampus for positive and negative memories

Comparison of the effect of retrieval focus also identified increased activity for positive (Emotion Positive > Context Positive) and decreased activity for negative (Emotion Negative < Context Negative) AMs in the left HC, in the Emotion condition (see **Figure 5** and **Table 2**). The decreased activity observed for the negative AMs in the left HC extended more posteriorly to the parahippocampal gyrus. Although similar overall patterns of activity were observed in the right HC, only the increased response for positive AMs when focusing on Emotion compared to Context was significant (Emotion Positive > Context Positive).

These effects were confirmed by repeated-measures ANOVAs performed on the extracted signal from peak voxels, which, in the left HC, revealed a significant valence x focus interaction [$F_{(1,16)} = 12.94$, $p = 0.002$]. This interaction was driven by a significant increase for positive memories ($p = 0.009$) and a significant decrease for negative memories ($p = 0.048$) in the Emotion compared to the Context condition. Similarly, the effect in the right HC was confirmed by a repeated-measures ANOVA revealing a significant valence x focus interaction [$F_{(1,16)} = 6.66$, $p = 0.02$], which was driven by a significant increase for positive memories ($p = 0.03$) in the Emotion compared to the Context condition.

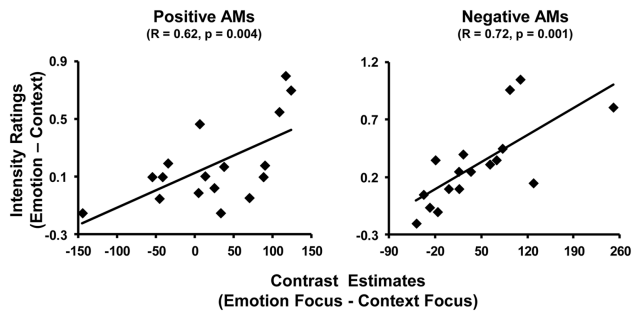


FIGURE 4 | Positive correlation between activity in the AMY and self-reported emotional ratings. Differential activity in the AMY for Emotion and Context focuses was positively related to the difference in emotion intensity ratings between Emotion and Context conditions during recollection of positive (left panel) and negative (right panel) memories. The scatter plots are based on contrast estimates for Emotion – Context conditions extracted from the peak voxel of the areas showing the co-variation with the differences in ratings, in the left AMY. Similar co-variations were also identified in right AMY (not shown).

EFFECTS OF RETRIEVAL FOCUS ON BRAIN REGIONS OUTSIDE OF THE MTL

While the primary focus in the present report concerns the effects of retrieval focus on the MTL activity during retrieving positive and negative AMs, for completeness, results of whole-brain analyses are also reported (see **Table 3**).

DISCUSSION

The present study investigated the behavioral and brain imaging effects of retrieval instructions, linked to the valence of memories, on AM recollection. There were four main findings, showing both similarities and differences in retrieving positive and negative AMs. Regarding similarities, (1) the behavioral data showed that focusing on Emotion was associated with increased scores of subjective re-experience of emotion, and the fMRI data identified increased activity in the left AMY, for both positive and negative AMs, compared to focusing on the Context; (2) the subjective emotional ratings were also positively correlated with bilateral AMY activity for both positive and negative AMs. Regarding differences, (3) focusing on Emotion was associated with increased activity for positive but not for negative AMs in the right AMY, and with (4) opposing patterns of activity linked to the valence of AMs in the left HC – i.e., increased activity for positive AMs and decreased activity for negative AMs. These findings will be discussed in turn below.

COMMON EFFECTS OF RETRIEVAL FOCUS ON POSITIVE AND NEGATIVE AM RETRIEVAL IN AMY

(1) Manipulation of the retrieval focus was associated with increased activity in the left AMY for both positive and negative memories in the Emotion compared to the Context condition.

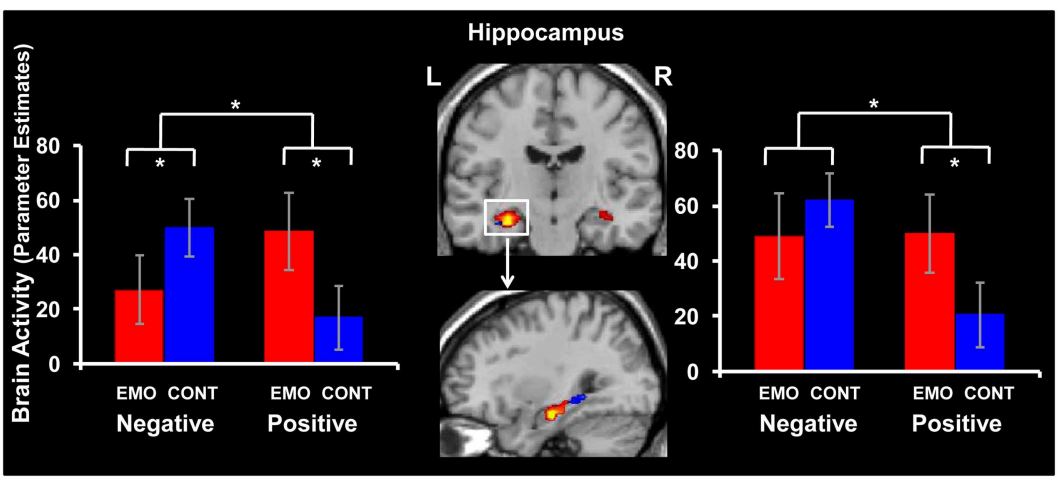


FIGURE 5 | Dissociable effects of retrieval focus in the hippocampus (HC) for positive and negative memories. Focusing on Emotion (EMO) compared to focusing on Context (CONT) led to increased activity for positive and decreased activity for negative memories in the left hippocampus (HC) (left panel). Although, overall, a similar effect was observed in the right HC (right panel), only the increased activity for positive memories was statistically significant. The interaction map for the left and right HC is superimposed on a high resolution brain image displayed in a coronal view (top panel). The sagittal view (bottom panel) illustrates the posterior extension of activity in the left HC (blue blob), for negative memories (Context Negative > Emotion Negative). The bar graphs represent the contrasts estimates extracted from representative voxels of the interaction effects in left and right HC. The error bars correspond to the standard errors of the means. L = Left, R = Right.

Table 3 | Whole-brain activations linked to retrieval focus and valence of memories.

Brain regions	BA	Side	Talairach coordinates			*T* score	Cluster size
			x	*y*	*z*		
A. DIRECT CONTRASTS							
Emotion Positive vs. Context Positive							
Inferior frontal gyrus	47	R	28	35	−5	6.08	54
Anterior cingulate	10	R	20	47	1	5.37	
Middle temporal gyrus	21	L	−56	0	−7	5.63	26
Superior temporal gyrus	38	L	−56	11	−7	4.83	
Precuneus	7	L	−4	−59	62	4.97	10
Inferior frontal gyrus	44	L	−55	12	10	4.91	10
Inferior frontal gyrus	47	L	−36	19	−8	4.85	41
Emotion Positive vs. Emotion Negative							
Precentral gyrus	4	L	−44	−18	34	4.68	11
Context Negative vs. Context Positive							
Inferior frontal gyrus	47	L	−36	19	−14	4.84	13
Hippocampus		L	−32	−12	−9	4.40	5
Hippocampus		R	32	−12	−13	4.47	5
B. INTERACTIONS							
(Emotion Positive vs. Context Positive) vs. (Emotion Negative vs. Context Negative)							
Middle temporal gyrus	21	L	−60	−4	−3	6.20	13
Hippocampus		L	−32	−16	−16	5.06	17
Caudate (tail)		L	−24	−42	13	4.98	24
Postcentral gyrus	3	L	−48	−18	34	4.51	28
Middle frontal gyrus	10	R	44	42	−5	4.40	14
(Context Negative vs. Emotion Negative) vs. (Context Positive vs. Emotion Positive)							
Caudate (tail)		L	−24	−42	13	4.98	13
Hippocampus		L	−36	−16	−16	3.60	7
(Emotion Positive vs. Emotion Negative) vs. (Context Positive vs. Context Negative):							
Hippocampus		L	−32	−16	−16	5.06	10
Cingulate gyrus	31	L	−24	−46	13	4.64	17
Postcentral gyrus	3	L	−48	−18	34	4.51	28
(Context Negative vs. Context Positive) vs. (Emotion Negative vs. Emotion Positive):							
Hippocampus		L	−32	−16	−16	5.06	19
Caudate (tail)		L	−24	−42	13	4.98	13
Postcentral gyrus	3	L	−48	−18	34	4.51	15
Middle frontal gyrus	10	R	40	42	−5	4.32	11

Significant activations resulting from whole-brain analyses investigating direct contrasts and interactions are reported. For direct contrasts, a threshold of $p < 0.001$ was used, and for interactions a threshold of $p < 0.005$ was used. For the interaction analyses, the interaction contrast was inclusively masked with the corresponding direct contrast set up at $p < 0.05$. A cluster size of 10 contiguous voxels was used in all analyses, except for the MTL, where a cluster size of 5 contiguous voxels was used. BA = Brodmann's area; L = left, R = right.

This finding is consistent with the emotion research suggesting that the AMY's engagement can be modulated by attention, current goals, and task demands (Blair et al., 2007; Lieberman et al., 2007; Shafer et al., 2012). Moreover, this finding extends the available evidence by revealing that this effect also applies to the retrieval of positive and negative AMs. This is important because the evidence that left AMY activity is susceptible to and acts in accordance with the current retrieval goals clarifies inconsistent findings regarding its involvement in previous AM studies. Typically, these studies emphasize the effortful reconstruction of personal episodes that occurred at a specific time and place (Maguire, 2001; Svoboda et al., 2006), and do not systematically or explicitly probe the emotionality of the recollected memories.

(2) The AMY activity was also positively correlated with the emotional intensity ratings in the Emotion vs. Context condition, so that greater engagement of the AMY when focusing on emotional compared to the contextual details was associated with greater subjective re-experience of emotion of the recollected AMs. This finding provides, therefore, a direct link between AMY activity and subjective affective re-experience, which was not observed in previous "standard" AM studies (Maguire and Frith, 2003; Addis et al., 2004) probably due to the absence of a clear emotional focus during retrieval.

DISSOCIABLE EFFECTS OF RETRIEVAL FOCUS ON POSITIVE AND NEGATIVE AM RETRIEVAL IN AMY AND HC

(3) Retrieval of positive AMs was associated with increased right AMY activity in the Emotion compared to the Context condition, while retrieval of negative AMs produced similar effects in the right AMY. The latter finding suggests that the right AMY activity is not modulated by the current retrieval goals in the case of negative AMs. This is in contrast to the left AMY activity, which is sensitive to the current retrieval goals in the case of both positive and negative AMs, and altogether these findings suggest a hemispheric dissociation in the AMY regarding to the retrieval focus during AM recollection. Available evidence points to various factors that may influence hemispheric asymmetries in emotion processing that may also affect AMY activity, including emotional valence (negative vs. positive) (Canli et al., 1998), memory processes (encoding vs. retrieval) (Sergerie et al., 2006), and level of processing (automatic vs. elaborated) (Morris et al., 1998; Glascher and Adolphs, 2003; Dyck et al., 2011; Ritchey et al., 2011).

The present AMY lateralization cannot be fully explained by valence effects alone, but could be linked to Glascher's and Adolphs' (2003) suggestion that the right AMY is involved in initial, automatic detection of emotions, whereas the left AMY is involved in more elaborated cognitive representation of emotions (see also Morris et al., 1999; Phelps et al., 2001). In the present study, it might be the case that because of its more automatic engagement in emotion detection and processing, and possibly because of different prioritization of processing negative emotions, the right AMY may be less susceptible to modulations of the retrieval focus during recollection of negative AMs. Hence, its response was similarly high regardless of whether the focus was on Emotion or on Context, which was not the case for positive AMs. This interpretation is also consistent with evidence of fast processing of negative stimuli in the AMY (Morris et al., 1999; Vuilleumier et al., 2001).

The absence of significant differences in AMY activity between positive and negative AMs retrieved with an Emotion focus is in line with a valence-independent role of the AMY in the detection and evaluation of relevant and salient emotions (Wager et al., 2008; Lindquist et al., 2012) and with evidence of its involvement in emotional personal recollections (Botzung et al., 2010; Staniloiu and Markowitsch, 2012). Overall, the present data are consistent with both a stronger left AMY engagement for positive and negative AMs, when there is an explicit emphasis on emotional aspects, and a differential right AMY engagement for positive and negative AMs, when emotional processing is not overtly demanded. These findings point to the interplay between emotional valence and retrieval focus, which if not considered together can lead to incomplete conclusions.

(4) Manipulation of the retrieval focus was associated with increased activity for positive and decreased activity for negative AMs in the left HC, in the Emotion condition. Given the evidence linking left hippocampal activity to more detailed recollections (Addis et al., 2004), a possible interpretation is that negative AMs in the Emotion condition are less detailed than the negative AMs in the Context condition. However, this interpretation is not consistent with the present behavioral results, which did not show differences in the scores for Vividness in the Emotion and Context conditions (3.37 and 3.32, respectively). A slightly more nuanced interpretation can be proposed if the effects observed in the HC are considered in the context of evidence regarding its role in processing visual landmarks (Berthoz, 1997) and in binding together contextual and scene-related details (Davachi et al., 2003; Davachi, 2006). Specifically, it could be speculated that greater involvement of the posterior portion of the HC may be solicited to bind contextual details that are detached from emotional aspects (i.e., negative AMs with Context focus). Therefore, the decrease in the left HC for negative memories in the Emotion condition (which had the highest intensity ratings) could be due to an automatic binding of details by arousal (Mather and Sutherland, 2011), which probably required less hippocampal involvement. However, in the case of positive AMs, probably attaining similar level of recollection required increased left hippocampal involvement when the retrieval focus was on Emotion.

Caveats

One limitation of the present study is the absence of a Neutral control condition, which limits the interpretation of the findings. This was mainly dictated by the difficulty in identifying enough neutral memories that could be equated with the emotional AMs in terms of their phenomenological properties. The inclusion of neutral memories in future studies could be used as an additional baseline to complement the present findings. Another limitation is that the number of subjects did not allow proper investigation of sex-related differences, which have been addressed in only a handful of AM neuroimaging studies (e.g., Piefke et al., 2005; St Jacques et al., 2011). Future studies should examine whether the effects of retrieval focus and valence are differently affected in women and men.

CONCLUSION

In summary, the present study reveals similar and differential involvement of the AMY and HC during the recollection of emotional personal memories, linked to the current retrieval goals and the valence of memories. By shedding light on the role of AMY and HC in these effects, the present findings clarify mixed or inconclusive findings of previous AMs studies in healthy participants, and have the potential to contribute to a better understanding and prevention of affective disorders, which are characterized by an excessive focus on negative AMs.

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REFERENCES

Addis, D. R., Moscovitch, M., Crawley, A. P., and McAndrews, M. P. (2004). Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus* 14, 752–762. doi:10.1002/hipo.10215

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016

Battig, W. F., and Montague, W. E. (1969). Category norms of verbal items in 56 categories a replication and extension of the connecticut category norms. *J. Exp. Psychol.* 80, 1–46. doi:10.1037/h0027577

Berthoz, A. (1997). Parietal and hippocampal contribution to topokinetic and topographic memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 352, 1437–1448. doi:10.1098/rstb.1997.0130

Blair, K. S., Smith, B. W., Mitchell, D. G., Morton, J., Vythilingam, M., Pessoa, L., et al. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage* 35, 430–440. doi:10.1016/j.neuroimage.2006.11.048

Bluck, S., and Alea, N. (2009a). Thinking and talking about the past: why remember? *Appl. Cogn. Psychol.* 23, 1089–1104. doi:10.1002/acp.1612

Bluck, S., and Alea, N. (2009b). Characteristics of positive autobiographical memories in adulthood. *Int. J. Aging Hum. Dev.* 69, 247–265. doi:10.2190/AG.69.4.a

Botzung, A., Denkova, E., Ciuciu, P., Scheiber, C., and Manning, L. (2008). The neural bases of the constructive nature of autobiographical memories studied with a self-paced fMRI design. *Memory* 16, 351–363. doi:10.1080/09658210801931222

Botzung, A., Rubin, D. C., Miles, A., Cabeza, R., and Labar, K. S. (2010). Mental hoop diaries: emotional memories of a college basketball game in rival fans. *J. Neurosci.* 30, 2130–2137. doi:10.1523/JNEUROSCI.2481-09.2010

Brewin, C. R., Reynolds, M., and Tata, P. (1999). Autobiographical memory processes and the course of depression. *J. Abnorm. Psychol.* 108, 511–517. doi:10.1037/0021-843X.108.3.511

Cabeza, R., and St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends Cogn. Sci.* 11, 219–227. doi:10.1016/j.tics.2007.02.005

Canli, T., Desmond, J. E., Zhao, Z., Glover, G., and Gabrieli, J. D. (1998). Hemispheric asymmetry for emotional stimuli detected with fMRI. *Neuroreport* 9, 3233–3239. doi:10.1097/00001756-199810050-00019

Daselaar, S. M., Rice, H. J., Greenberg, D. L., Cabeza, R., LaBar, K. S., and Rubin, D. C. (2008). The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. *Cereb. Cortex* 18, 217–229. doi:10.1093/cercor/bhm048

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr. Opin. Neurobiol.* 16, 693–700. doi:10.1016/j.conb.2006.10.012

Davachi, L., Mitchell, J. P., and Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2157–2162. doi:10.1073/pnas.0337195100

Denkova, E., Botzung, A., Scheiber, C., and Manning, L. (2006). Implicit emotion during recollection of past events: a nonverbal fMRI study. *Brain Res.* 1078, 143–150. doi:10.1016/j.brainres.2006.01.061

Denkova, E., Dolcos, S., and Dolcos, F. (2012). Reliving emotional personal memories: affective biases linked to personality and sex-related differences. *Emotion* 12, 515–528. doi:10.1037/a0026809

Denkova, E., Wong, G., Dolcos, S., Sung, K., Wang, L., Coupland, N., et al. (2010). The impact of anxiety-inducing distraction on cognitive performance: a combined brain imaging and personality investigation. *PLoS ONE* 5:e14150. doi:10.1371/journal.pone.0014150

Dolcos, F., Denkova, E., and Dolcos, S. (2012). Neural correlates of emotional memories: a review of evidence from brain imaging studies. Special issue on recent advances of functional neuroimaging studies on episodic memories. *Psychologia* 55, 80–111. doi:10.2117/psysoc.2012.80

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 42, 855–863. doi:10.1016/S0896-6273(04)00289-2

Dolcos, F., LaBar, K. S., and Cabeza, R. (2005). Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proc. Natl. Acad. Sci. U.S.A.* 102, 2626–2631. doi:10.1073/pnas.0409848102

Dolcos, F., and McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *J. Neurosci.* 26, 2072–2079. doi:10.1523/JNEUROSCI.5042-05.2006

Dyck, M., Loughead, J., Kellermann, T., Boers, F., Gur, R. C., and Mathiak, K. (2011). Cognitive versus automatic mechanisms of mood induction differentially activate left and right amygdala. *Neuroimage* 54, 2503–2513. doi:10.1016/j.neuroimage.2010.10.013

Finnbogadottir, H., and Berntsen, D. (2012). Involuntary future projections are as frequent as involuntary memories, but more positive. *Conscious. Cogn.* 22, 272–280. doi:10.1016/j.concog.2012.06.014

Glascher, J., and Adolphs, R. (2003). Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. *J. Neurosci.* 23, 10274–10282.

Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., and Labar, K. S. (2005). Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia* 43, 659–674. doi:10.1016/j.neuropsychologia.2004.09.002

Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* 2, 289–293. doi:10.1038/6404

Joormann, J., Siemer, M., and Gotlib, I. H. (2007). Mood regulation in depression: differential effects of distraction and recall of happy memories on sad mood. *J. Abnorm. Psychol.* 116, 484–490. doi:10.1037/0021-843X.116.3.484

Josephson, B. R., Singer, J. A., and Salovey, P. (1996). Mood regulation and memory: repairing sad moods with happy memories. *Cogn. Emot.* 10, 437–444. doi:10.1080/026999396380222

Kensinger, E. A., and Corkin, S. (2004). Two routes to emotional memory: distinct neural processes for valence and arousal. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3310–3315. doi:10.1073/pnas.0306408101

Kensinger, E. A., and Schacter, D. L. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *J. Neurosci.* 26, 2564–2570. doi:10.1523/JNEUROSCI.5241-05.2006

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychol. Aging* 17, 677–689. doi:10.1037/0882-7974.17.4.677

Lieberman, M. D., Eisenberger, N. I., Crockett, M. J., Tom, S. M., Pfeifer, J. H., and Way, B. M. (2007). Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol. Sci.* 18, 421–428. doi:10.1111/j.1467-9280.2007.01916.x

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., and Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 35, 121–143. doi:10.1017/S0140525X11000446

MacLeod, A. K., and Byrne, A. (1996). Anxiety, depression, and the anticipation of future positive and negative experiences. *J. Abnorm. Psychol.* 105, 286–289. doi:10.1037/0021-843X.105.2.286

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1441–1451. doi:10.1098/rstb.2001.0944

Maguire, E. A., and Frith, C. D. (2003). Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. *J. Neurosci.* 23, 5302–5307.

Maguire, E. A., and Mummery, C. J. (1999). Differential modulation of a common memory retrieval network revealed by positron emission tomography. *Hippocampus* 9, 54–61. doi:10.1002/(SICI)1098-1063(1999)9:1<54::AID-HIPO6>3.0.CO;2-O

Markowitsch, H. J., and Staniloiu, A. (2011). Amygdala in action: relaying biological and social significance to autobiographical memory. *Neuropsychologia* 49, 718–733. doi:10.1016/j.neuropsychologia.2010.10.007

Markowitsch, H. J., Thiel, A., Reinkemeier, M., Kessler, J., Koyuncu, A., and Heiss, W. D. (2000). Right amygdalar and temporofrontal activation during autobiographic, but not during fictitious memory retrieval. *Behav. Neurol.* 12, 181–190.

Markowitsch, H. J., Vandekerckhove, M. M., Lanfermann, H., and Russ, M. O. (2003). Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. *Cortex* 39, 643–665. doi:10.1016/S0010-9452(08)70858-X

Mather, M., and Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.* 6, 114–133. doi:10.1177/1745691611400234

Mor, N., and Winquist, J. (2002). Self-focused attention and negative affect: a meta-analysis. *Psychol. Bull.* 128, 638–662. doi:10.1037/0033-2909.128.4.638

Morris, J. S., Ohman, A., and Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature* 393, 467–470. doi:10.1038/30976

Morris, J. S., Ohman, A., and Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc. Natl. Acad. Sci. U.S.A.* 96, 1680–1685. doi:10.1073/pnas.96.4.1680

Nolen-Hoeksema, S., Wisco, B. E., and Lyubomirsky, S. (2008). Rethinking rumination. *Perspect. Psychol. Sci.* 3, 400–424. doi:10.1111/j.1745-6924.2008.00088.x

Ochsner, K. N., and Schacter, D. L. (2000). "A social cognitive neuroscience approach to emotion and memory," in *The Neuropsychology of Emotion*, ed. J. C. Borod (New York: Oxford University Press), 163–193.

Pennebaker, J. W., and Graybeal, A. (2001). Patterns of natural language use: disclosure, personality, and social integration. *Curr. Dir. Psychol. Sci.* 10, 90–93. doi:10.1111/1467-8721.00123

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Grillon, C., Gore, J. C., and Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nat. Neurosci.* 4, 437–441. doi:10.1038/86110

Piefke, M., Weiss, P. H., Markowitsch, H. J., and Fink, G. R. (2005). Gender differences in the functional neuroanatomy of emotional episodic autobiographical memory. *Hum. Brain Mapp.* 24, 313–324. doi:10.1002/hbm.20092

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., and Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain* 126(Pt 3), 650–668. doi:10.1093/brain/awg064

Rasmussen, A. S., and Berntsen, D. (2013). The reality of the past versus the ideality of the future: emotional valence and functional differences between past and future mental time travel. *Mem. Cognit.* 41, 187–200. doi:10.3758/s13421-012-0260-y

Ritchey, M., Dolcos, F., and Cabeza, R. (2008). Role of amygdala connectivity in the persistence of emotional memories over time: an event-related FMRI investigation. *Cereb. Cortex* 18, 2494–2504. doi:10.1093/cercor/bhm262

Ritchey, M., LaBar, K. S., and Cabeza, R. (2011). Level of processing modulates the neural correlates of emotional memory formation. *J. Cogn. Neurosci.* 23, 757–771. doi:10.1162/jocn.2010.21487

Sergerie, K., Lepage, M., and Armony, J. L. (2006). A process-specific functional dissociation of the amygdala in emotional memory. *J. Cogn. Neurosci.* 18, 1359–1367. doi:10.1162/jocn.2006.18.8.1359

Shafer, A. T., Matveychuk, D., Penney, T., O'Hare, A. J., Stokes, J., and Dolcos, F. (2012). Processing of emotional distraction is both automatic and modulated by attention: evidence from an event-related fMRI investigation. *J. Cogn. Neurosci.* 24, 1233–1252. doi:10.1162/jocn_a_00206

Sharot, T., Riccardi, A. M., Raio, C. M., and Phelps, E. A. (2007). Neural mechanisms mediating optimism bias. *Nature* 450, 102–105. doi:10.1038/nature06280

Smith, A. P., Stephan, K. E., Rugg, M. D., and Dolan, R. J. (2006). Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron* 49, 631–638. doi:10.1016/j.neuron.2005.12.025

Smith, J. M., and Alloy, L. B. (2009). A roadmap to rumination: a review of the definition, assessment, and conceptualization of this multifaceted construct. *Clin. Psychol. Rev.* 29, 116–128. doi:10.1016/j.cpr.2008.10.003

St Jacques, P. L. (2012). "Functional neuroimaging of autobiographical memory," in *Understanding Autobiographical Memory: Theories and Approaches*, eds D. Bernsten, and D. C. Rubin (Cambridge: Cambridge University Press), 114–138.

St Jacques, P. L., Conway, M. A., and Cabeza, R. (2011). Gender differences in autobiographical memory for everyday events: retrieval elicited by SenseCam images versus verbal cues. *Memory* 19, 723–732. doi:10.1080/09658211.2010.516266

Staniloiu, A., and Markowitsch, H. J. (2012). A rapprochement between emotion and cognition: amygdala, emotion, and self-relevance in episodic-autobiographical memory. *Behav. Brain Sci.* 35, 164–166. doi:10.1017/S0140525X11001543

Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208. doi:10.1016/j.neuropsychologia.2006.05.023

Szpunar, K. K., Addis, D. R., and Schacter, D. L. (2012). Memory for emotional simulations: remembering a rosy future. *Psychol. Sci.* 23, 24–29. doi:10.1177/0956797611422237

Vandekerckhove, M. M., Markowitsch, H. J., Mertens, M., and Woermann, F. G. (2005). Bi-hemispheric engagement in the retrieval of autobiographical episodes. *Behav. Neurol.* 16, 203–210.

Vuilleumier, P., Armony, J. L., Driver, J., and Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron* 30, 829–841. doi:10.1016/S0896-6273(01)00328-2

Wager, T. D., Barrett, L. F., Bliss-Moreau, E., Lindquist, K., Duncan, S., Kober, H., et al. (2008). "The neuroimaging of emotion," in *The Handbook of Emotion*, eds M. Lewis, J. M. Haviland-Jones, and L. F. Barrett, 3rd Edn. (New York: Guilford), 249–271.

Wilson, T. D., and Gilbert, D. T. (2008). Explaining away: a model of affective adaptation. *Perspect. Psychol. Sci.* 3, 370–386. doi:10.1111/j.1745-6924.2008.00085.x

Young, K. D., Bellgowan, P. S., Bodurka, J., and Drevets, W. C. (2012). Functional neuroimaging of sex differences in autobiographical memory recall. *Hum. Brain Mapp.* doi:10.1002/hbm.22144

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Dissociating retrieval success from incidental encoding activity during emotional memory retrieval, in the medial temporal lobe

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The memory-enhancing effect of emotion has been linked to the engagement of emotion- and memory-related medial temporal lobe (MTL) regions (amygdala-AMY; hippocampus-HC; parahippocampus-PHC), during both encoding and retrieval. However, recognition tasks used to investigate the neural correlates of retrieval make it difficult to distinguish MTL engagement linked to retrieval success (RS) from that linked to incidental encoding success (ES) during retrieval. This issue has been investigated for retrieval of non-emotional memories, but not for emotional memory retrieval. To address this, we used event-related functional MRI in conjunction with an emotional distraction and two episodic memory tasks (one testing memory for distracter items and the other testing memory for new/lure items presented in the first memory task). This paradigm allowed for dissociation of MTL activity specifically linked to RS from that linked to both RS and incidental ES during retrieval. There were two novel findings regarding the neural correlates of emotional memory retrieval. First, greater emotional RS was identified bilaterally in AMY, HC, and PHC. However, AMY activity was most impacted when accounting for ES activity, as only RS activity in left AMY was dissociated from ES activity during retrieval, whereas portions of HC and PHC showing greater emotional RS were largely uninvolved in ES. Second, an earlier and more anteriorly spread response (left AMY and bilateral HC, PHC) was linked to greater emotional RS activity, whereas a later and more posteriorly localized response (right posterior PHC) was linked to greater neutral RS activity. These findings shed light on MTL mechanisms subserving the memory-enhancing effect of emotion at retrieval.

Keywords: affect, recollection, episodic memory, successful retrieval, incidental learning

INTRODUCTION

Investigations on the impact of emotion on memory have shown that emotion enhances memory (Bradley et al., 1992; Christianson, 1992; Chiu et al., 2013), and that this enhancement is associated with increased engagement of emotion (amygdala, AMY) and memory (hippocampus, HC and parahippocampus, PHC) related medial temporal lobe (MTL) regions. This increased engagement is observed during both encoding (Dolcos et al., 2004; McGaugh, 2004; Dolcos and Denkova, 2008; Murty et al., 2011) and retrieval (Sharot et al., 2004; Dolcos et al., 2005; Kensinger and Schacter, 2005; Sergerie et al., 2006; Smith et al., 2006); reviewed in Dolcos et al. (2012). While the MTL's role in encoding success (ES) operations contributing to the memory-enhancing effect of emotion has been well documented, open questions still remain concerning its role in emotional memory retrieval. One unclear aspect concerns the dissociation between neural activity linked to retrieval success (RS) processes and activity associated with encoding processes that occur during retrieval. Due to the nature of recognition memory tasks used to study the neural correlates of memory retrieval, it is unclear whether MTL regions identified as being associated with retrieval processes are unique to retrieval or are common to both successful retrieval and incidental encoding that occurs during retrieval. The present study addressed this issue by using functional magnetic resonance imaging (fMRI) in conjunction with an experimental design that allowed for the dissociation of MTL involvement in retrieval success from incidental encoding success, during the retrieval of emotional memories.

Investigations of MTL activity associated with incidental memory formation during non-emotional memory retrieval (Stark and Okado, 2003) found that MTL regions associated with neutral retrieval success largely overlapped with those involved in the incidental encoding of lure items. Even though a large amount of overlap was found, specificity within the HC was also found such that areas in the HC were identified as being associated with retrieval success after accounting for incidental encoding during retrieval. However, to our knowledge similar investigations have not been performed during emotional memory retrieval. Therefore, it remains unclear whether or not activity linked to the memory-enhancing effect of emotion identified in

MTL-based emotion and memory regions during retrieval can be distinguished from activity related to the memory-enhancing effect of emotion associated with incidental memory formation during retrieval. Hence, the first goal of the present investigation was to address this issue by identifying MTL activity specifically related to the successful retrieval of emotional memories that does not contribute to incidental encoding during emotional memory retrieval.

Recognition memory tasks involve various aspects of processing, including retrieval operations *per se*, re-encoding/consolidation of retrieved memories, and incidental encoding of new information presented as lures. The focus of the present investigation is to distinguish between MTL areas subserving memory operations that contribute to the successful retrieval of information from MTL areas involved in incidental memory formation during retrieval. It should be noted that in the context of the present investigation we refer to "encoding operations" from a mnemonic not perceptual perspective. The former refer to memory-specific processing that leads to the formation of new memories, whereas the latter refer to general perceptual processing that occurs regardless of subsequent memory effects. There are currently two methodological approaches regarding the identification of the neural correlates of retrieval success. One compares activity for old items correctly identified as old (Hits) and activity for old items incorrectly identified as new (Misses), and the other compares activity for Hits and new items correctly identified as new (Correct Rejections, CR).

We defined retrieval success activity as resulting from the comparison between Hits and Misses, because the comparison between Hits and CR makes it difficult to distinguish between various aspects of processing during retrieval. For example, if a brain region is involved in both retrieval success *per se* and incidental encoding success during retrieval, then the incidental encoding success activity in response to a lure item that was correctly rejected may equate the retrieval success activity in response to an Old item that was remembered. In this situation a brain region would erroneously show no involvement in retrieval success activity, because it contributes to both aspects of processing. This has previously been shown for the involvement of MTL regions in non-emotional memory retrieval and incidental encoding (Stark and Okado, 2003).

One way to identify incidental encoding success activity, and dissociate it from retrieval success activity, is to use a second subsequent memory task (second retrieval task) and compare brain activity for Misses that are subsequently remembered to Misses that remain forgotten. However, this contrast cannot control for the effects associated with repeated presentation of these items, which may eventually lead to their encoding into memory. Therefore, it is difficult to determine if later memory for Misses that were initially forgotten during the first retrieval task and then remembered during the second retrieval task is due to successful encoding during the first retrieval or due to a repeated exposure effect where the signal for a particular item may finally surpass the criteria necessary for an old response.

To avoid repeated presentation, we favor an alternative way of identifying and dissociating incidental encoding success activity from retrieval success activity. This involves comparison of activity for new items/lures presented during the first retrieval task that are then remembered or forgotten in a subsequent memory task (second retrieval task). In this regard, incidental encoding success activity during retrieval refers to the successful encoding of items presented as lures during the first retrieval task. Using this approach allows for the separation of retrieval success activity, obtained by comparing Hits and Misses, from incidental encoding success activity resulted from the contrast between the remembered lures and forgotten lures (in the second retrieval task).

Previous investigations of the neural mechanisms of emotional memory have pointed to spatial and temporal dissociations. Regarding the former, fMRI investigations have identified an anterior-posterior dissociation in the MTL, with emotional memory involving more anterior regions (AMY and anterior HC, PHC regions) and neutral memory involving more posterior regions (middle to posterior HC and PHC) (Dolcos et al., 2004; Sharot et al., 2004; Kensinger and Schacter, 2005; Dougal et al., 2007). Regarding temporal dissociations, event-related potential (ERP) studies have pointed to earlier memory-related processing contributing to the memory-enhancing effect of emotion compared to that contributing to non-emotional memory (Dolcos and Cabeza, 2002). Although this finding is consistent with previous research highlighting faster processing of emotional information (Dolcos and Cabeza, 2002; Larson et al., 2006; Mendez-Bertolo et al., 2013), it is uncertain if these timing differences can also be observed in the BOLD response within the MTL during retrieval, especially given that the temporal resolution offered by fMRI is less than ideal for determining the temporal characteristics of cognitive processes. Nevertheless, when using fMRI, some information concerning their timing may still be gleaned (Siegle et al., 2002; Larson et al., 2006; Daselaar et al., 2008; Schuyler et al., 2012). For example, emotional and neutral retrieval activity may possess similar magnitudes, but time to peak onset of those magnitudes may differ, thus revealing dissimilarities between the associated neural mechanisms of these processes that would otherwise remain hidden when not considering the time course of the BOLD response. To that end, the second goal of the present investigation was to explore the possibility of differences in the time course of the BOLD response for emotional and neutral retrieval activity in the MTL.

These issues were addressed by using an experimental design in which participants sequentially performed three tasks to identify and compare the neural correlates of retrieval success to those associated with incidental encoding success during retrieval. First, participants performed a perception task that served as the "study phase" for the items used to examine the neural correlates of retrieval. Then, immediately following the perception task, participants performed an episodic memory task that served as the "test phase" for the items used to examine the neural correlates of retrieval as well as the "study phase" for lure items used to identify the neural correlates of incidental encoding during retrieval. Lastly, participants performed another episodic memory task that served as the "test phase" for the lures that were presented during the first episodic memory task (see **Figure 1**). For the current investigation we restricted our analyses to regions within the MTL. This was done for three reasons. First, MTL

engagement in memory processes is among the most systematic findings in the literature regarding the neuroscience of memory; hence, we targeted this region due to its reliable involvement in the processes under investigation. Second, while other non-MTL brain regions (e.g., frontal and parietal cortices) are also contributing to the memory-enhancing effect of emotion, their involvement tends to be mediated by the contribution of other processes, such as attention, working memory, and semantic memory (Dolcos et al., 2012; Shafer and Dolcos, 2012). In contrast, MTL regions are less susceptible to such influences due to their relatively automatic engagement during the encoding and retrieval of emotional memories (Ritchey et al., 2011; Shafer and Dolcos, 2012). Third, we primarily sought to build on the existing literature concerning the present research topic, where there was focus only on MTL-based memory regions for non-emotional memories (Stark and Okado, 2003).

Based on the extant evidence we made the following three predictions: Concerning the first main goal and consistent with previous research examining the influence of emotion on memory, we predicted enhanced memory for emotional relative to neutral items, during both memory tasks. Regarding the fMRI findings and based on earlier research for non-emotional memory (Stark and Okado, 2003), we predicted that the memory-enhancing effect of emotion at retrieval would be at least partially accounted for by activity related to memory-enhancing effect of emotion associated with incidental encoding during retrieval. Concerning the second main goal, and based on previous findings showing that encoding processes associated with the memory-enhancing effect of emotion occur earlier (Dolcos and Cabeza, 2002) and influence more anterior MTL regions (Dolcos et al., 2004), we explored the possibility that similar differences could also be identified at retrieval, with emotional retrieval success activity occurring earlier and in more anterior MTL regions than the neutral retrieval success activity.

METHODS

PARTICIPANTS

Data from a group of 17 healthy young adults [19–33 years of age ($M = 23.11$, $SD = 4.01$); 10 females; all right-handed] were analyzed for the present investigation. Data from all 17 participants was used to examine the influence of emotion on immediate memory. Data from 10 participants (19–33 years of age, $M = 24.6$, $SD = 4.53$, 7 female) was used to examine the influence of emotion on delayed memory in order to examine incidental encoding during retrieval. Participants were recruited from the Edmonton City area, provided written informed consent before participating, and were reimbursed for their participation. The experimental protocol was approved for ethical treatment of the human participants by the Institutional Health Research Board.

TASKS AND STIMULI

Each participant performed a perceptual orientation discrimination task and an episodic memory task (EM-1), while brain imaging data were collected using fMRI (Shafer and Dolcos, 2012; Shafer et al., 2012). One-week following the completion of these two tasks, participants also performed a delayed episodic memory task (EM-2) for items that were presented as lures during the immediate episodic memory task (see task diagram illustrated in **Figure 1**). In the perceptual orientation discrimination task, participants made decisions on the orientation of vertical and horizontal pictures with negative and neutral content. In the memory task immediately following the perception task, participants made decisions about whether emotional and neutral pictures had been presented during the perception task (Old) or they had not been seen before (New). In the delayed memory task, performed 5–7 days after the completion of the first two tasks, participants made decisions about whether or not emotional and neutral pictures were presented as lures during the immediate episodic memory task or were New items that had not been seen before. All of the emotional and neutral pictures were selected from the International Affective Pictures System (Lang et al., 2008), based on normative arousal and valence ratings and from in-house pictures used in previous studies (Yamasaki et al., 2002; Dolcos and McCarthy, 2006). For each individual task, valence and arousal scores were significantly different for emotional and neutral pictures. Notably, the arousal and valence scores did not differ across tasks within emotional or neutral picture categories. Since our main goal focused on effects associated with the overall emotional charge, rather than on identifying the relative contribution of basic emotional dimensions (arousal vs. valence), the present results cannot distinguish between the contribution of these two affective dimensions to the observed effects.

Perception task

The stimuli and design of the perception task are identical to those described previously (Shafer et al., 2012). Briefly, the perception task manipulated the attentional demand necessary to determine the orientation of vertically or horizontally presented pictures that contained emotional (negative), non-emotional (neutral), or no distraction (scrambled). The mean arousal (1 = Lowest/9 = Highest) and valence (1 = Very Negative, 5 = Neutral, 9 = Very Positive) scores for the 224 pictures used during the perception task, respectively, were as follows: 5.9/2.75, for emotional pictures; 3.35/5.05 for neutral pictures. Participants were instructed to determine the orientation of the rectangles, to maintain focus on the orientation task, and to respond as accurately and quickly as possible.

Episodic Memory task 1 (EM-1)

The stimuli and design of the immediate episodic memory task are identical to those described previously (Shafer and Dolcos, 2012). Briefly, EM-1 was a surprise memory task for items that were presented as distracters during the perception task. This task consisted of 160 pictures, which were a sub-set of the 224 pictures presented in the initial perception task. These Old images were pseudo-randomized with 80 New pictures (40 emotional, 40 neutral) that were selected on normative arousal and valence scores and semantic content from the same picture databases used for the perception task. The average normative arousal and valence scores for Old and New emotional and neutral pictures for the first episodic memory task were as follows: 5.93/2.63 for emotional Old pictures; 5.95/2.66 for emotional New pictures;

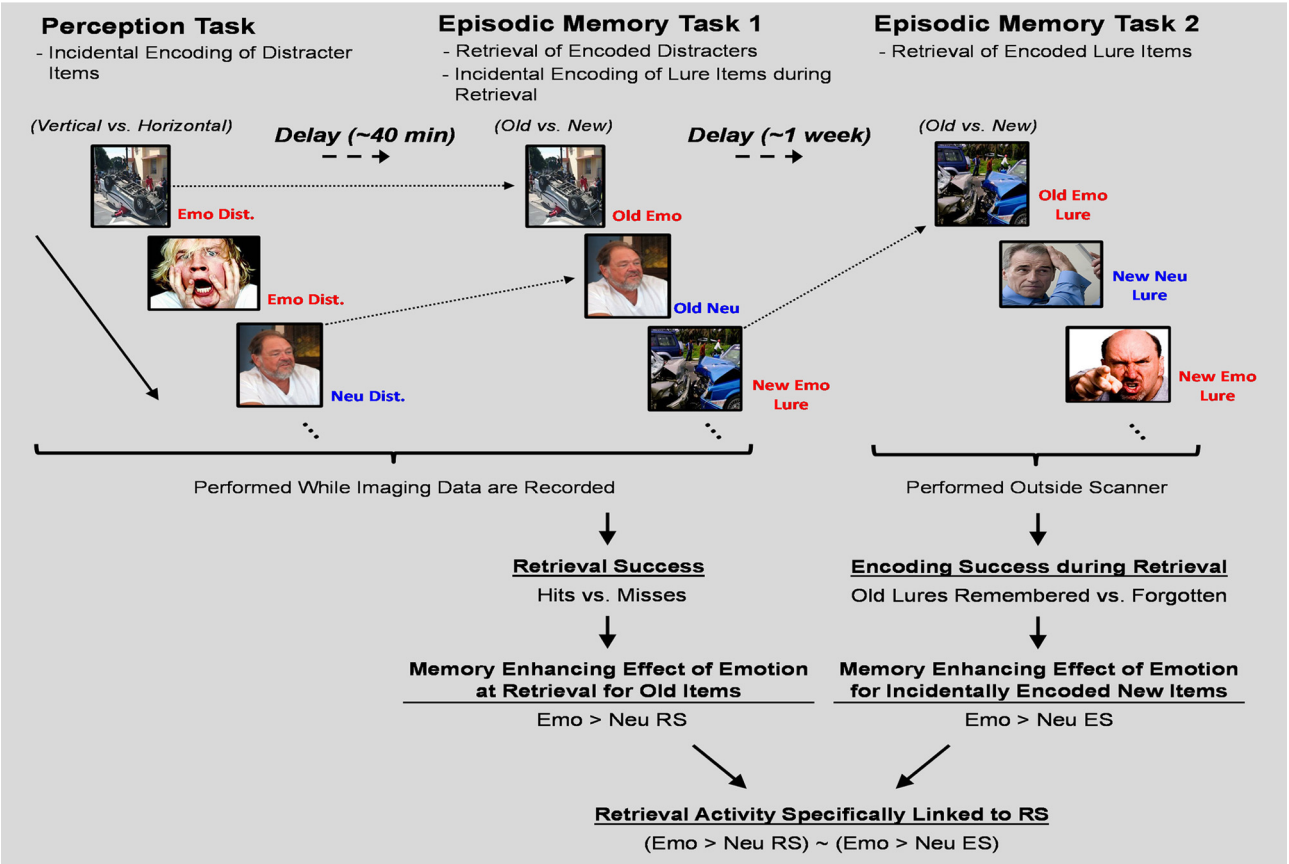


FIGURE 1 | Diagram of the experimental paradigm. A novel experimental paradigm was implemented to investigate the relationship between retrieval success activity and incidental encoding success activity during retrieval. The perception task required participants to determine the orientation of vertically or horizontally presented pictures with emotional, neutral, or no distraction. Immediately following completion of the perception task, memory for a subset of the pictures presented as distracters during the task was tested in a surprise episodic memory task (EM-1). EM-1 allowed for the examination of the neural correlates of retrieval success of the distracter items incidentally encoded during the perception task, and also served as the "study" phase for emotional and neutral lure items. Approximately 1 week following the completion of the perception and EM-1 tasks, participants completed another surprise episodic memory task (EM-2), which tested memory for the emotional and neutral lure items used during EM-1. In both memory tasks participants were instructed to determine if the pictures were from the previous task (Old) or never seen before (New). Old/New decisions were followed by confidence ratings (1 = low, 2 = medium, 3 = high). Separation of RS from incidental ES activity was obtained by defining RS as the contrast between Hits and Misses and incidental ES as the contrast between Remembered and Forgotten Lure items. Emo, Emotional; Neu, Neutral; Dist., Distracter; RS, Retrieval Success; ES, Encoding Success

3.41/5.04, for neutral Old pictures; and 3.41/5.02 for neutral New pictures. To ensure a minimum retention interval for the memory-enhancing effect of emotion to occur, a minimum delay of 20 min between the initial encoding and first retrieval task was imposed (Kleinsmith and Kaplan, 1963). Participants were randomly assigned one of two run orders which allowed for a similar delay period between encoding and retrieval. This was essential to the overall design of the paradigm as Old stimuli in the first episodic memory task were pseudo-randomized based on when they appeared in the perception task. This resulted in a delay of approximately 40 min between the encoding and retrieval of a stimulus. For example, if a picture was presented in the first run of the perception task, then it would be presented in either the first or second run of the recognition task. Likewise, if a stimulus was presented in the last run of the perception task then it was presented in the second to last or last run of the recognition task.

Episodic Memory task 2 (EM-2)

Approximately 1-week (Range = 5–7 days; Mean = 6.8) following the completion of the perception and EM-1 tasks, participants performed an episodic memory task for items that were presented as lures during EM-1. The 80 Old pictures that served as lures during EM-1 were pseudo-randomized with 40 (20 emotional, 20 neutral) New lure pictures. Old and New pictures did not statistically differ in normative arousal and valence, other than between the emotional and neutral pictures – negative pictures were significantly more negative and arousing than neutral pictures. The average normative arousal and valence scores for Old and New emotional and neutral pictures for the second episodic memory task were as follows: 5.95/2.66 for emotional Old pictures; 5.91/2.46 for emotional New pictures; 3.41/5.02, for neutral Old pictures; and 3.52/5.00 for neutral New pictures.

EXPERIMENTAL PROCEDURES

After the first experimental session (consisting of the perception and EM-1 tasks) participants were asked to return to the lab for further testing in one-week. The procedure for EM-1 is identical to that described in Shafer and Dolcos (2012). Approximately one-week later, 14 participants returned and completed EM-2 outside of the scanner. The test included a total of 120 pictures (80 Old, 40 New) distributed across 5 runs (24 pictures/run). To avoid mood induction, trials were pseudo-randomized such that no more than two consecutive trials of the same valence type occurred. As with EM-1, each picture was displayed for 2 s during which participants had to indicate with a button press whether the picture was Old, presented during EM-1 or New, not presented in EM-1. Immediately following the 2 s response window, a confidence rating screen was presented for 2 s asking participants to indicate the level of confidence (LOC) for their decision on a three-point Likert scale (1 = lowest, 3 = highest). Each trial was followed by a jittered fixation interval drawn from an exponential distribution with a median of 6 s (Range = 4–12 s). Similar to EM-1, participants were not informed of the EM-2 task. During both memory tasks participants were instructed to respond accurately and quickly, and that if they were unsure if a picture was Old or New to provide their best guess and indicate that their decision was uncertain by assigning that trial a low confidence rating.

IMAGING PROTOCOL

MRI data were collected on a 1.5-T Siemens Sonata scanner. After the sagittal localizer and the 3-D MPRAGE anatomical images (TR = 1600 ms; TE = 3.82 ms; FOV = 256 × 256 mm; number of slices = 112, voxel size = 1 mm^3), EPI functional volumes allowing for full brain coverage were acquired axially (TR = 2000 ms; TE = 40 ms; FOV = 256 × 256 mm; number of slices/volume = 28, voxel size = 4 × 4 × 4 mm).

BEHAVIORAL ANALYSES

Responses in EM-1 and EM-2 tasks were classified into one of four categories [Hits – Old pictures correctly identified as Old; Misses – Old pictures incorrectly identified as New; CRs – New pictures correctly identified as New; False Alarms (FAs) – New pictures incorrectly identified as Old], as derived from signal detection theory (Macmillan and Creelman, 1991). These categories were used to calculate corrected recognition (% Hits – % FAs) scores. Since the main goal of the present investigation was to distinguish between the neural correlates of retrieval success and incidental encoding success during retrieval, all trials from the perception task were included in the data analysis for EM-1 (i.e., regardless of whether they were associated with correct or incorrect responses in the perception task). Previous analyses of this data set focused on brain imaging data acquired during the perception task and results focused on emotional distraction and encoding success for correct trials were published elsewhere (Shafer and Dolcos, 2012; Shafer et al., 2012). To maximize the difference in the MTL response during retrieval between remembered and forgotten items, only items that were given a LOC of 3 were included in the data analyses for both EM-1 and EM-2 tasks (Kleinsmith and Kaplan, 1963; Yonelinas, 2001; Daselaar et al., 2006). To assess the influence of emotion on memory performance, emotional and neutral corrected recognition scores were entered into a paired samples *t*-test. This was done separately for EM-1 and EM-2. To determine if differences in the delay period between EM-1 and EM-2 affected memory performance corrected recognition scores across the two tasks were examined using repeated measures analyses of variance (ANOVA) for the 10 participants who had both EM-1 and EM-2 data. Task (EM-1, EM-2), Valence (Emo, Neu), and Memory (Hit, Miss) were within-subject variables. *Post-hoc* comparisons were performed, where appropriate, and Bonferroni corrected.

fMRI ANALYSES

Statistical analyses were preceded by the following preprocessing steps (performed with SPM2 – Statistical Parametric Mapping): TR alignment, motion correction, normalization, and smoothing (8 mm kernel). For the data analysis, we used in-house custom MATLAB scripts involving both whole-brain voxel-wise and region-of-interest (ROI) analyses to compare brain activity associated with conditions of interest. For subject-level analyses, the fMRI signal was selectively averaged for each participant as a function of trial type (i.e., emotional hits, emotional misses, neutral hits, neutral misses, remembered emotional lures, forgotten emotional lures, remembered neutral lures, forgotten neutral lures) and time point (or TR; one pre- and 8 post-stimulus onset) using custom MATLAB scripts. Pair-wise *t* statistics for the contrasts of interest were calculated for each subject; no assumption was made about the shape of the hemodynamic response function (Dolcos and McCarthy, 2006; Dolcos et al., 2008; Morey et al., 2009). Individual analyses produced whole-brain activation *t* maps for each condition, contrast of interest, and TR/time point (TP). The outputs of the subject-level analyses were used as inputs for the second-level, random-effects within-group analyses.

REGION OF INTEREST (ROI) ANALYSES

Identification of brain activity linked to retrieval success and the incidental encoding success of lure items

Of the fourteen participants that completed EM-2, only 10 participants met the criteria for inclusion when examining the number of trials per condition for LOC 3 responses. Criteria for inclusion required that each participant have at least five (Huettel and McCarthy, 2001) good trials (raw MR signal ≥ 300 MR units) per trial type, associated with high level of confidence (LOC 3) ratings. Thus, imaging data analyses assessing the neural correlates of retrieval success were performed on data from 17 participants, while imaging data analyses assessing the neural correlates of incidental encoding success were performed on data from 10 participants. To identify MTL activity linked to the memory-enhancing effect of emotion, analyses directly comparing brain activity between emotional and neutral retrieval/encoding success [i.e., (emotional vs. neutral Hits – Misses)/(emotional vs. neutral Remembered – Forgotten Lure Items), respectively] were performed on trials where behavioral differences were observed and where memory strength is the strongest (i.e., LOC 3 trials). Brain regions associated with emotional (Emotional Hits > Misses) and neutral (Neutral Hits > Misses) memory were separately identified for each time point. These contrasts for emotional and neutral retrieval/encoding success were then entered into a

paired samples *t*-test which was then inclusively masked by the main effect of emotional retrieval/encoding success (Emotional Hits > Misses). This procedure allowed identification of MTL regions where activity for emotional retrieval/encoding success was greater than for neutral retrieval/encoding success, for each time point [i.e., ((Emotional Hits-Misses) vs. (Neutral Hits-Misses)) ∩ (Emotional Hits-Misses)]. The inclusive masking of the interaction (or conjunction analyses) identified greater retrieval success for emotional than for neutral pictures [i.e., (Emotional Hits > Misses) > (Neutral Hits > Misses)]. This was necessary to ensure that the interaction difference occurred in regions also showing significant retrieval success activity for the emotional pictures (Emotional Hits > Misses). This is a more conservative procedure in identifying differences between retrieval success activity for emotional and neutral material because it eliminates areas where such differences could be driven by the absence of retrieval success activity for emotional stimuli (e.g., if activity for Emotional Hits is not significantly greater than for Emotional Misses), coupled with effects going in opposite direction for the neutral pictures (Neutral Misses > Neutral Hits). To identify MTL regions where the response for neutral memory was greater than the response to emotional memory contrasts for neutral retrieval/encoding success were entered into a paired samples *t*-test which was then inclusively masked by the main effect of neutral retrieval/encoding success [i.e., ((Neutral Hits-Misses) vs. (Emotional Hits-Misses)) ∩ (Neutral Hits-Misses)].

Conjunction analyses involved masking procedures performed in MATLAB using the logical function AND. Thus, only voxels that met the threshold criteria in each of the contributing *t* maps survived the masking procedure. This procedure is consistent with the conjunction null hypothesis testing (Nichols et al., 2005). In addition, areas of activation were corrected for multiple comparisons in two ways. We applied two levels of false discovery rate (FDR) corrections, one corresponding to a *p*-value of 0.05 (Genovese et al., 2002) for each anatomical ROI, and the other corresponding to a *p*-value of 0.05 for each functional cluster within anatomically restricted ROIs (i.e., restricted to the anatomical boundaries of the MTL ROIs) – see **Tables 1**, **2**. The present procedure involving FDR corrections and conjunction analyses, along with the reporting of both corrected and uncorrected statistical values offer a good balance between the cost of potential Type I and II errors (Lieberman and Cunningham, 2009). The greatest effect in MTL regions for emotional and neutral retrieval/encoding success occurred from time points 5–7 (6–10 s after stimulus onset). MTL activity for these time points was isolated using the Automated Anatomical Labeling atlas (AAL, Tzourio-Mazoyer et al., 2002) in SPM for the HC and PHC. These were used in conjunction with an in-house AMY mask (Dolcos et al., 2004; Moore et al., 2014) which corrected for large discrepancies in the AAL AMY mask.

Dissociating retrieval processes linked to the memory-enhancing effect of emotion

MTL activity observed across time points of greatest activity (time points 5–7), as identified in the individual analyses for incidental encoding success, was merged in MATLAB using the logical function OR. This was done separately for emotional and neutral items, to identify and collapse all significant areas of activation for each of the peak time points. For example, the clusters of activation identified in the MTL for emotional incidental encoding success (Emotional Lures Remembered-Forgotten) at time points 5, 6, and 7 were combined into one t-map representing MTL activity for emotional incidental encoding success and for the memory-enhancing effect of emotion incidental encoding success [((Emotional Lures Remembered-Forgotten) vs. (Neutral Lures Remembered-Forgotten)) ∩ (Emotional Lures Remembered-Forgotten)]. This same process was applied to *t* maps for neutral encoding success activity and neutral > emotional encoding success activity. Due to the low number of participants contributing to the analyses identifying incidental encoding success activity during retrieval, we implemented the incidental encoding success results as binary maps to identify areas showing retrieval success activity that have no contribution to incidental encoding success activity during retrieval. Specifically, we made the group *t*-maps identified by the steps mentioned above for emotional, neutral, emotional > neutral, and neutral > emotional incidental encoding success into binary masks. That is, voxels were assigned a value of 1 if *p*-values were less than or equal to 0.05, and all other voxels within the ROIs not meeting this criterion were given a value of zero. For each ROI, *t*-maps corresponding to emotional, neutral, emotional > neutral, and neutral > emotional retrieval success activity were then exclusively masked with this binary mask [e.g., (Emotional Hits > Misses) ∼ (Emotional Lure Hits > Lure Misses), (Neutral Hits > Misses) ∼ (Neutral Lure Hits > Lure Misses)], and regions surviving these masking procedures were identified (see **Tables 1, 2**). MTL activity for emotional, neutral, emotional > neutral, and neutral > emotional retrieval success *t*-maps after exclusively masking for activity associated with incidental encoding success was isolated using the AAL atlas in SPM for the HC and PHC. These were used in conjunction with an in-house AMY mask (Dolcos et al., 2004; Moore et al., 2014).

Exploratory analysis investigating possible temporal and spatial dissociations between emotional and neutral retrieval success

After exclusively masking by incidental encoding success activity during retrieval, functional ROIs from within region clusters for emotional greater than neutral retrieval success activity, and neutral greater than emotional retrieval success activity (e.g., right anterior PHC and right posterior PHC, respectively) were used to extract the fMRI signal for each participant, for each condition, and time point. These data were then entered into a repeated measures ANOVAs assessing Memory (Hits, Misses), Valence (Emotional, Neutral), and Time Point (5, 6, and 7). A significant three-way interaction in a region was further investigated at each time point for a Memory by Valence interaction. Follow-up *post-hoc* comparisons were performed, where appropriate, and Bonferroni corrected.

RESULTS

BEHAVIORAL RESULTS

Increased memory for emotional pictures

To maximize the difference in response to remembered and forgotten items in the brain imaging data, only trials that were given

Table 1 | MTL regions engaged in emotional and neutral retrieval success.

MTL regions	Hemisphere	Talairach coordinates			*t*-values Cluster corrected	Cluster size	Time (s)
		x	*y*	*z*			
EMOTIONAL RS							
AMY	L	−19	0	−14	**6.17**¶ *	62	6
		−30	−8	−11	**5.06**¶ *		6
		−23	−8	−11	**4.58**¶ *	5	8
		−30	8	−17	**3.57**	24	8
		−19	4	−14	**2.75***		8
	R	29	4	−13	**5.5**¶	46	6
		21	4	−17	**4.63**¶		6
		14	0	−10	**4.31**¶		6
		25	4	−17	**3.11**	15	8
HC	L	−23	−23	−9	**5.38**¶ *	69	6
		−34	−11	−12	**5.07**¶ *		6
		−19	−11	−12	**3.92**¶ *		6
		−30	−11	−15	**4.62***	59	8
		−19	−15	−12	**3.54**		8
		−16	−27	−6	**2.73**		8
		−30	−11	−15	**2.69***	8	10
	R	29	−12	−7	**3.81**¶	69	6
		18	−4	−17	**3.35**¶		6
		21	−27	−5	**3.26**¶		6
		32	−20	−8	**3.35***	10	8
PHC	L	−19	0	−18	**6.18**¶ *	70	6
		−23	−22	−20	**5.33**¶ *		6
		−16	−35	−6	**2.56**¶		6
		−16	4	−14	**4.08***		8
		−31	−34	−10	**3.85**		8
		−27	−18	−20	**3.3***		8
		−19	−27	−9	**2.69***		8
	R	14	−3	−21	**3.66**¶	18	6
		14	4	−13	**3.5**¶ *		6
		25	−31	−9	**3.51**¶ *	22	6
NEUTRAL RS							
AMY	L	−23	−1	−7	**2.51***	27	6
		−23	8	−21	**2.41***		6
		−19	0	−14	**2.17**		6
		−16	−8	−11	**3.74***	22	8
		−27	0	−14	**2.49***		8
		−19	4	−14	**1.89***		8
		−16	−4	−11	**3.05***	35	10
		−27	−4	−15	**2.8***		10
		−30	1	−21	**2.69***		10
	R	18	−1	−6	**2.84***	15	6
		21	0	−13	**2.18***	10	8
HC	L	−31	−20	−5	**2.92**	5	6
		−30	−15	−12	**4.07***	42	8

(Continued)

Table 1 | Continued

MTL regions	Hemisphere	Talairach coordinates			*t*-values Cluster corrected	Cluster size	Time (s)
		x	*y*	*z*			
		−27	−11	−12	**3.75***	22	10
		−30	−3	−18	**3.09**		10
	R	14	−35	1	**3.06***	16	6
		21	−24	−5	**2.17**		6
		25	−39	1	**2.56**	11	8
		14	−31	−2	**2.27**		8
		18	−12	−11	**2.43***	6	8
		21	−19	−12	**1.97***		8
		32	−15	−11	1.96*	6	8
		32	−23	−8	1.86*		8
		21	−31	−2	**2.48**	7	10
		21	−39	1	**2.46**		10
		32	−12	−11	**2.26**	7	10
PHC	L	−16	4	−14	**3.19***	10	6
		−34	−14	−23	**3.12**	5	8
		−16	−7	−15	**3***	5	8
		−19	−23	−13	**2.1***	5	8
		−23	−15	−16	**2.07***		8
		−19	−23	−13	2.61	5	10
		−19	−15	−15	2.4		10
	R	21	−39	−3	**3.75**	6	8
		21	−39	−3	**3.27**	17	10
		18	−26	−16	**3.26***		10

*The table identifies MTL regions where emotional and neutral RS are significant. The displayed t-values correspond to the peak voxel for each time point after stimulus onset (where the HDR response was maximal), and represents a significant difference in MR signal between remembered and forgotten items. Emotional RS = (Emotional Hits-Misses) and Neutral RS = (Neutral Hits-Misses). *regions surviving exclusive masking by incidental encoding. ¶region surviving FDR-anatomical ROI correction. MTL, medial temporal lobe; AMY, amygdala; HC, hippocampus; PHC, parahippocampus; L, left; R, right; RS, retrieval success; HDR, hemodynamic response; MR, magnetic resonance; Cluster Cor., False Discovery Rate-cluster correction. Cluster corrected values are indicated in bold.*

the highest level of confidence (LOC 3) were used for analyses (Kleinsmith and Kaplan, 1963; Yonelinas, 2001; Daselaar et al., 2006). Analyses of corrected recognition scores for LOC 3 trials for EM-1 showed that emotional pictures ($M = 0.23$, $SE = 0.03$) were better remembered than the neutral pictures ($M = 0.17$, $SE = 0.04$), [$t_{(16)} = 1.85$, $p = 0.04$, one-tailed]. Mean hit and FA rates for LOC 3 trials in the first episodic memory task for emotional/neutral pictures were as follows: 0.56 ($SD = 0.13$)/0.37 ($SD = 0.18$) and 0.33 ($SD = 0.14$)/0.19 ($SD = 0.11$), respectively. Similarly, analyses of corrected recognition scores for LOC 3 trials for EM-2 showed that memory for emotional lures ($M = 0.19$, $SE = 0.05$) was better than memory for neutral lures ($M = 0.04$, $SE = 0.04$), [$t_{(9)} = 4.12$, $p = 0.001$]. For the second episodic memory task mean hit and FA rates for emotional/neutral pictures were: 0.43 ($SD = 0.12$)/0.23 ($SD = 0.11$) and 0.24 ($SD = 0.14$)/0.19 ($SD = 0.1$), respectively. These analyses identified greater memory for emotional than neutral pictures in both EM tasks, with a numerically greater emotion effect following longer delay (Dolcos et al., 2005; Ritchey et al., 2008)—see **Figure 2A**. To investigate whether this interaction between emotional memory and EM task was significant a repeated measures ANOVA with the variables Task, Valence, and Memory was performed on the 10 participants who met the LOC 3 criterion for EM-2. The impact of emotion on memory was found to increase by 46% from EM-1 to EM-2. However, this increase across tasks was not statistically significant [$F_{(1, 9)} = 1.44$, $p = 0.26$]. Interestingly though, and consistent with research showing emotional memories persist better over time compared to neutral memory (Dolcos et al., 2005; Ritchey, 2008; Ritchey et al., 2008), this apparent change in the impact of emotion on memory across tasks was not due to an increase in emotional memory *per se* [$t_{(9)} = 0.82$, $p = 0.43$], but because of a decrease of the neutral memory in the second episodic memory task [$t_{(9)} = 2.37$, $p = 0.04$] – see **Figure 2B**.

fMRI RESULTS

Dissociating retrieval processes linked to the memory-enhancing effect of emotion

To examine MTL activity associated with the memory-enhancing effect of emotion at retrieval, we first contrasted activity for emotional remembered and forgotten items, and neutral remembered

Table 2 | MTL regions specifically engaged in emotional vs. neutral retrieval success activity.

MTL regions	Hemisphere	Talairach coordinates			*t*-values Cluster corrected	Cluster size	Time (s)
		x	*y*	*z*			
EMOTIONAL > NEUTRAL RS							
AMY	L	−19	0	−14	**3.84***	23	6
		−30	−8	−11	**2.88***		6
	R	27	4	−13	**4.16**	5	6
		14	0	−17	**2.56**	6	6
HC	L	−23	−39	4	**3.3***	27	6
		−30	−7	−15	**2.62***		6
		−20	−27	−6	**2.26***		6
	R	18	−11	−18	**3.85***	28	6
PHC	L	−23	−22	−20	**5.75¶***	6	6
		−19	−30	−10	**3.61***	50	6
		−16	0	−12	**6.32***		6
		−27	−22	−23	**2.56***	7	8
	R	21	−11	−22	**3.62***	36	6
		18	−34	−9	**3.54***		6
		14	4	−13	**2.61***		6
NEUTRAL > EMOTIONAL RS							
HC	R	25	−39	1	**2.87**	7	8
		21	−31	−2	**3.09**	7	10
PHC	R	18	−26	−19	**2.92***	13	10
		17	−39	−3	**2.38***		10

*The table identifies MTL regions where emotional RS was greater than neutral RS and where neutral RS was greater than emotional RS. The displayed t-values correspond to the peak voxel for each time point after stimulus onset (where the HDR response was maximal), and represents a significant difference in MR signal between emotion RS and neutral RS. Emotional > Neutral RS = [((Emotional Hits-Misses)—(Neutral Hits-Misses)) ∩ (Emotional Hits-Misses)]. Neutral > Emotional RS = [((Neutral Hits-Misses)—(Emotional Hits-Misses)) ∩ (Neutral Hits-Misses)]. Extent threshold = 5 voxels. ¶regions surviving FDR-anatomical ROI correction. *regions surviving exclusive masking by incidental encoding. MTL, medial temporal lobe; AMY, amygdala; HC, hippocampus; PHC, parahippocampus; L, left; R, right; RS, retrieval success; Cluster Cor., False Discovery Rate-cluster correction. Cluster corrected values are indicated in bold.*

and forgotten items. Increased activity throughout the MTL was identified in response to emotional and neutral memory (see **Table 1**). Next, to examine the memory-enhancing effect of emotion at retrieval, we contrasted activity for emotional and neutral memory [(Emo Hits > Misses) > (Neu Hits > Misses)]. Replicating previous findings of the involvement of MTL regions in the retrieval of emotional items (Dolcos et al., 2005), emotional compared to neutral retrieval success resulted in greater activity in bilateral AMY, HC, and PHC (see **Table 2**). When examining retrieval-related activity without accounting for activity related to incidental encoding success during retrieval, three clusters of activity were identified in the AMY. A left hemisphere cluster extended through the entire amygdala and two right hemisphere clusters, one located laterally and the other medially. Two clusters of activity were identified in the HC. A right hemisphere cluster localized more anteriorly and a left hemisphere cluster that extended the entire length of the HC and contained an anterior, middle, and posterior peak. The PHC contained two clusters of activity in response to emotional greater than neutral retrieval success, one left and one right. Both clusters extended throughout the PHC and contained three peaks: anterior, middle, and posterior.

To investigate MTL activity dissociating retrieval success from incidental encoding successes during retrieval, linked to the memory-enhancing effect of emotion we exclusively masked retrieval activity by incidental encoding activity [((Emo Hits > Misses) > (Neu Hits > Misses)) ∼ ((Emo Lures Remembered > Forgotten) > (Neu Lures Remembered > Forgotten))]. MTL retrieval success activity related to the memory-enhancing effect of emotion that survived exclusive masking by incidental encoding success activity related to the memory-enhancing effect of emotion was identified in the left AMY, bilateral HC, and PHC (see **Table 2** and **Figure 3A**). For AMY, the two right hemisphere clusters identified for retrieval success also contributed to incidental encoding success. For the HC and PHC, partial activity within each of the clusters identified for retrieval success also contributed incidental encoding success during retrieval. However, all of the cluster peaks identified for retrieval success survived the exclusive masking procedure.

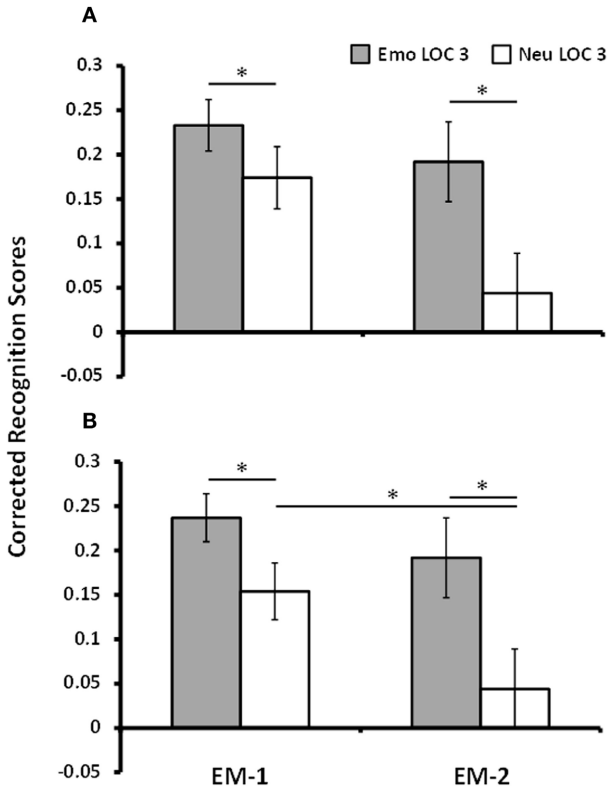


FIGURE 2 | Increased memory for emotional pictures. Figure shows corrected recognition scores for Emo and Neu LOC 3 items for EM-1 (left) and EM-2 (right). Memory performance was greater for Emo items than for Neu items in EM-1 and EM-2 **(A)**, which was also identified when tested with the subset of participants that had both EM-1 and EM-2 data **(B)**. There was a significant decrease in memory performance for neutral items from EM-1 to EM-2. Emo, Emotional; Neu, Neutral; LOC, Level of Confidence; EM-1, Episodic Memory task 1; EM-2, Episodic Memory task 2. * indicates *p*-value < 0.05, one-tailed.

In addition, investigation of MTL areas with greater sensitivity to neutral than to emotional retrieval [(Neu Hits > Misses) > (Emo Hits > Misses)], identified the right posterior HC and PHC. To determine whether this retrieval-related activity contributed to the incidental encoding of neutral lure items, we exclusively masked retrieval-related by incidental encoding-related activity [((Neu Hits > Misses) > (Emo Hits > Misses)) ∼ ((Neu Lures Remembered > Forgotten) > (Emo Lures Remembered > Forgotten))].

Activity surviving the exclusive masking procedure was located in the right posterior PHC (see **Table 2** and **Figures 3B,C**). Right posterior HC activity was found to contribute to both retrieval and incidental encoding success of neutral lure items during retrieval.

Exploratory analysis investigating possible temporal and spatial dissociations between emotional and neutral retrieval success

To examine differences in the temporal dynamics for retrieval processes linked to the enhancement of emotional memory vs. increased engagement for neutral memory (as observed in **Table 2**), we investigated changes in retrieval success activity over the peak time points of activation (time points 5–7). Sub-regions of the MTL sensitive to the enhancement of emotional memory or increased engagement for neutral memory that survived exclusive masking by encoding success activity during retrieval (see **Table 2**), showed earlier modulation for the enhancing effect of emotion (left AMY, bilateral HC and PHC) and later modulation for increased engagement associated with neutral memory (right posterior PHC) – see **Figure 4**. Regarding spatial dissociation, although greater emotional than neutral retrieval success activity was identified in AMY, HC, and PHG, regions showing greater neutral than emotional retrieval success activity were restricted to more posterior regions of the MTL (PHC) (see **Table 2**).

DISCUSSION

The present study used a novel experimental paradigm to dissociate between retrieval and incidental encoding success activity during emotional retrieval in the MTL. Two novel findings regarding the neural correlates of emotional retrieval were identified. First, greater emotional retrieval success activity was identified bilaterally in AMY, HC, and PHC. However, AMY activity was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success activity were largely uninvolved in encoding success. Second, an earlier and more anteriorly spread response (in left AMY and bilateral HC and PHC) was linked to greater emotional retrieval success, whereas a later and more posteriorly localized response (in right posterior PHC) was linked to increased engagement associated with neutral retrieval success. These findings are discussed in turn below.

DISSOCIATING RETRIEVAL PROCESSES LINKED TO THE MEMORY-ENHANCING EFFECT OF EMOTION

Memory performance for emotional relative to neutral items for EM-1 and EM-2 replicates findings from a large body of extant research examining item-based emotional memory (for review, see Dolcos et al., 2012; Chiu et al., 2013). Although the impact of emotion on memory for EM-1 is numerically weaker than that found for EM-2, specific aspects of the present study's design can account for this difference. First, EM-1 tested memory for items that were presented as task-irrelevant distracters during initial encoding. Thus, divided attentional resources between processing these task-irrelevant items and those required for performing the main perceptual task most likely resulted in a decrease in overall memory performance (Uncapher and Rugg, 2005). Furthermore, the emotional distracter items that served as memoranda in EM-1 were most difficult to ignore during the perception task. As a result, participants may have engaged mechanisms to minimize their influence on the perception task more than those required for performing the perception task in the presence of neutral distraction. Hence, increased engagement of these mechanisms might have also contributed to the decreased impact of emotion on memory, compared to EM-2. Second,

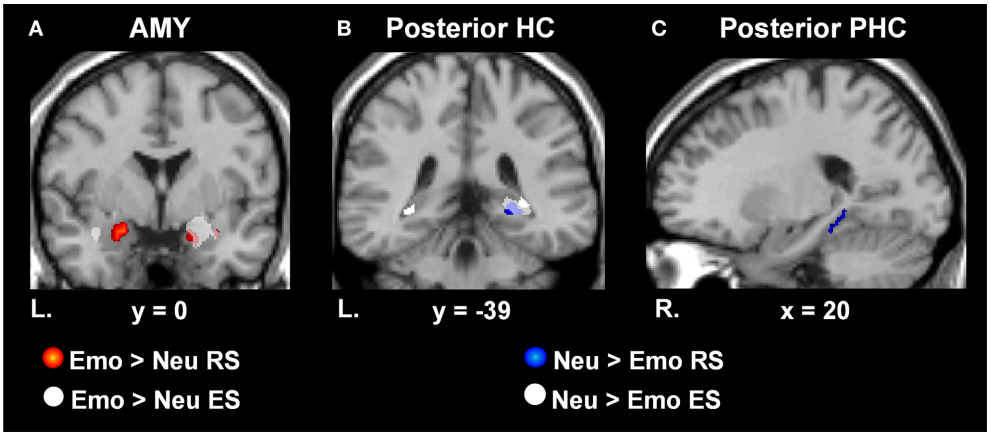


FIGURE 3 | Dissociating retrieval processes linked to the enhancement of emotional memory and increased engagement associated with neutral memory. MTL regions sensitive to Emo vs. Neu RS (red) and incidental ES (white) of Emo vs. Neu lure items presented during EM-1. Bilateral AMY activity was identified for Emo > Neu RS, but activity in the right hemisphere was accounted for by incidental Emo > Neu ES activity **(A)**. MTL regions showing greater RS activity for Neu > Emo items (blue) and incidental ES activity for Neu > Emo lure items (white) presented during EM-1. Right HC tail activity was identified for Neu > Emo RS, but was accounted for by encoding-related activity for lures during retrieval **(B)**. RS activity identified in the right posterior PHC, was unaccounted for by encoding related activity **(C)**. Areas indicated in red illustrate the difference in activation in response to Emo > Neu RS, masked with the main effect of Emo RS. Areas indicated in white on panel **(A)** illustrate activation in response to Emo > Neu ES, masked with the main effect of Emo ES. Areas indicated in blue illustrate the difference in activation in response to Neu > Emo RS, masked with the main effect of Neu RS. The *t*-values correspond to the *t* map for Neu > Emo RS. Areas indicated in white on panels **(B,C)** illustrate the activation in response to Neu > Emo ES, masked with the main effect of Neu ES. These activation maps are superimposed on a high-resolution brain image displayed in coronal **(A,B)** and sagital **(C)** views. The Talairach x and y coordinates for the corresponding plane is indicated below each high-resolution brain image. AMY, Amygdala; HC, hippocampus; PHC, Parahippocampus; MTL, Medial Temporal Lobe; RS, Retrieval Success; ES, Encoding Success; Emo, Emotional; Neu, Neutral; L, Left; R, Right; EM-1, Episodic Memory task 1.

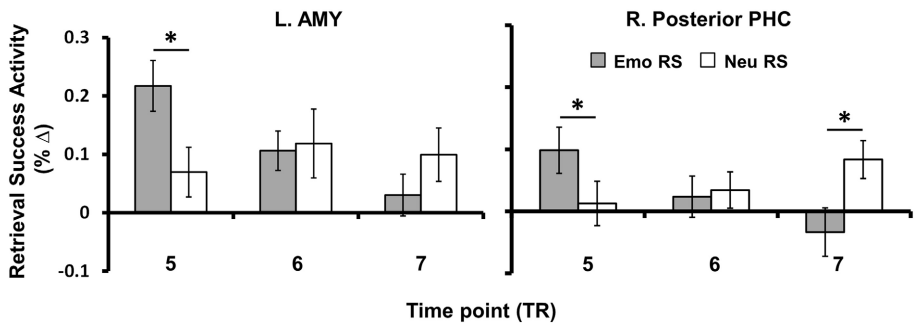


FIGURE 4 | Anterior-posterior and early-late dissociations identified for enhancement of Emotional vs. Neutral RS. MTL regions linked to the enhancement of memory for emotional or neutral items (i.e., those surviving exclusive masking as shown in **Table 2**) showed spatial and temporal differences in the BOLD responses. Regarding the spatial dissociation, Emo > Neu RS was identified in anterior, middle, and posterior regions of the MTL (AMY, HC, and PHC), whereas Neu > Emo RS was identified only in posterior PHC. Regarding the early-late dissociation, MTL activity linked to memory enhancement for emotional items was found at an earlier time point after stimulus onset, whereas MTL activity linked to memory enhancement for neutral items occurred at a later time point. Bar graphs illustrates the fMRI signal as extracted from the AMY and posterior PHC clusters corresponding to the difference in activation between hits and misses for emotional and neutral items, for TP five (6–8 s post-stimulus onset), six (8–10 s post-stimulus onset), and seven (10–12 s post-stimulus onset). Asterisks indicate that the difference between Hits and Misses (i.e., RS) was significantly greater for emotional than for neutral conditions or vice-versa. Error bars represent standard errors of means. AMY, Amygdala; HC, Hippocampus; PHC, Parahippocampal Cortex; BOLD, Blood-Oxygen-Dependent-Response; RS, Retrieval Success; TP, Time Point; TR, Repetition Time; Emo, Emotional; Neu, Neutral; L, Left; R, Right; $^{*}p < 0.05$, two-tailed.

although expected to be effective (Kleinsmith and Kaplan, 1963; Dolcos et al., 2004), our short retention interval (∼40 min) between encoding and retrieval of a single item also made a difference compared to the longer retention interval for EM-2 (Dolcos et al., 2005; Ritchey et al., 2008). Considering these aspects of the present design, the behavioral effect observed in EM-1 highlights the robustness of emotion's impact on memory, as it was present in conditions where the memoranda were task-irrelevant during initial encoding and when the retention interval was short.

Our result showing the persistence of emotional memory over time is also consistent with a number of earlier behavioral and

neuroimaging studies (Kleinsmith and Kaplan, 1963; Sharot and Phelps, 2004; Dolcos et al., 2005; Anderson et al., 2006; Ritchey et al., 2008; Sharot and Yonelinas, 2008). Enhanced memory performance for emotional relative to neutral items was associated with increased engagement of all three main regions of the MTL (AMY, HC, and PHC) during retrieval, which replicates previous neuroimaging studies of emotional retrieval (Sharot et al., 2004; Dolcos et al., 2005; Kensinger and Schacter, 2005; Sergerie et al., 2006; Smith et al., 2006).

The first novel finding of the present study involved the identification of MTL sub-regions that survived exclusive masking by incidental encoding success processes co-occurring during retrieval. When considering this finding in the context of the various aspects of processing that occur during retrieval (including retrieval operations *per se*, re-encoding/consolidation of retrieved memories, and incidental encoding of new information presented as lures), the current investigation offers insight into MTL sub-regions that may distinguish between retrieval operations and other memory operations occurring during retrieval (specifically, the encoding of new information presented during retrieval). As mentioned earlier, encoding operations can refer to general perceptual processing or to mnemonic processing that leads to the formation of new memories. As implemented here, one way of distinguishing between incidental encoding activity during retrieval from activity specifically linked to retrieval, while controlling for repeated exposure effects is to (1) define retrieval success as the difference in activity between Hits and Misses, and (2) compare activity for remembered vs. forgotten New items that were presented as lures during retrieval. This approach allows for the comparison of brain activity related to memory operations involved in successful retrieval of Old items, to brain activity related to memory operations involved in successful encoding of New items during retrieval. Using this approach, we found greater emotional retrieval success activity in bilateral AMY, HC, and PHC. However, AMY activity was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success activity were largely uninvolved in encoding success.

Retrieval processes have long been thought to involve the reactivation of encoding activity (Nyberg et al., 2000; Johnson and Rugg, 2007) and neuroimaging research has provided much support for this idea, with numerous studies showing that successful memory performance is associated with encoding-retrieval overlap in activations (Nyberg et al., 2000; Wheeler et al., 2000; Johnson and Rugg, 2007; Johnson et al., 2009; Ritchey et al., 2013). Moreover, emotional arousal has been shown to strengthen the relationship between memory performance and encoding-retrieval overlaps (Ritchey et al., 2013). Thus, it is reasonable to expect that successful encoding and retrieval of emotional memories involves similar mechanisms. However, the dissociation in MTL mechanisms during retrieval linked to retrieval success from those linked to encoding success demonstrate that it is possible to clarify the MTL's involvement in different memory operations that occur during recognition memory tasks. Open questions remain, however, regarding the mechanisms involved in the re-encoding/consolidation of emotional memories during retrieval (Nader and Einarsson, 2010).

EXPLORATORY ANALYSIS INVESTIGATING POSSIBLE TEMPORAL AND SPATIAL DISSOCIATIONS BETWEEN EMOTIONAL AND NEUTRAL RETRIEVAL SUCCESS

The second novel finding from the current study identified MTL regions where differences in the temporal dynamics of the BOLD response were found, with an earlier response to emotional enhancement of memory (left AMY, bilateral HC, and PHC) and a later response to increased engagement associated with neutral memory (right posterior PHC). This finding provides support for earlier research showing that the neural mechanisms subserving encoding of emotional memories are more quickly engaged than for neutral information (Dolcos and Cabeza, 2002; Larson et al., 2006; Mendez-Bertolo et al., 2013). Importantly, the current data extend these findings by showing that similar differences in timing are also present at retrieval. It is well known that emotion enhances the magnitude of early and late neural markers of stimulus processing, as shown by ERP studies (Olofsson et al., 2008), although shifts in the latency of ERP components indexing sensory and cognitive processes influenced by emotion are not commonly found (e.g., though this may be the result of event-related averaging vs. single-trial variability for ERP data). Also, negative emotions can produce faster responses of the oculomotor system resulting in quicker localization of threat (Bannerman et al., 2009, 2012). As also shown in the present results, fMRI studies of emotion processing can show differences in the temporal dynamics of the BOLD response between experimental conditions. These differences account for variance that would otherwise remain unexplained. However, these results should be treated with caution given the relatively poor temporal resolution of fMRI. More light will be shed on this topic as neuroimaging techniques advance to allow for the direct comparison and/or integration of more superior temporal techniques with more superior spatial techniques (e.g., simultaneous recordings of EEG and fMRI).

We also identified activation within the MTL showing greater neutral compared to emotional retrieval success. This activation was restricted to posterior HC and PHC regions. Only one cluster, right posterior PHC, survived exclusive masking by encoding success activity. Posterior MTL involvement in neutral greater than emotional retrieval success is consistent with previous research showing an anterior (emotional)—posterior (neutral) dissociation in the MTL during emotional memory encoding (Dolcos et al., 2004; Dougal et al., 2007) and retrieval (Sharot et al., 2004; Kensinger and Schacter, 2005). The reasons for this anterior-posterior dissociation remain unknown, but it has been suggested that this dissociation may be linked to the location relative to the AMY, with the anterior memory-related MTL regions being closer to the AMY and thus more involved in emotional memory due to rich interconnections between the AMY and anterior HC/PHC. The involvement of anterior MTL during emotional memory retrieval is consistent with the modulation hypothesis (McGaugh, 2004) of emotional memory encoding and consolidation, and with evidence from

previous studies of emotional retrieval. The modulation hypothesis suggests that AMY exerts neuromodulatory influences on other brain regions (e.g., the MTL memory system) involved in memory formation. Our result showing more anterior MTL engagement during emotional memory retrieval is consistent with earlier reports on emotional retrieval (Dolcos et al., 2005; Kensinger and Schacter, 2005; Sergerie et al., 2006; Smith et al., 2006), where the functional interactions supported by the modulation hypothesis for encoding and consolidation are extended to retrieval (LaBar and Cabeza, 2006). While the neurobiological mechanisms underlying AMY-MTL memory system functional interactions during retrieval remain largely unclear, they have begun to be elucidated by psychopharmacological and animal studies. For instance, research showing the β-adernergic blockade of the memory-enhancing effect of emotion during retrieval (Kroes et al., 2010) and increased synchronization between AMY and HC during fear retrieval (Seidenbecher et al., 2003) suggest that the neuromodulatory role of the AMY in emotional memory is similar for encoding, consolidation, and retrieval. This is consistent with the current findings showing overlap between retrieval success and encoding success activity during retrieval. However, and as shown here, research also suggests that certain aspects of the processes occurring during retrieval can be dissociated (Stark and Okado, 2003), which is consistent with evidence from animal research (Nader and Einarsson, 2010). On the other hand, posterior HC/PHC regions due to their more remote location from the AMY may not be as susceptible to its modulatory influences, and hence their involvement in neutral memory is not "overshadowed" by emotion's influence. Instead, these areas are closer to regions associated with visual processing, and thus are perhaps more involved in item processing that engages the ventral visual stream (Ungerleider, 1995; Dolcos et al., 2004). Although the current findings show some posterior HC and PHC involvement for the memory-enhancing effect of emotion, the majority of MTL regions identified for this analysis were more anteriorly located, whereas increased MTL engagement for neutral relative to emotional memory was restricted to posterior regions. Future research is needed to clarify the causes of this dissociation.

CAVEATS

A limitation of the present study is the number of participants contributing to the incidental encoding success analyses. Equal numbers of participants contributing to both retrieval success and encoding success analyses would have been ideal in providing increased specificity when dissociating MTL activity linked to different memory processes during retrieval. Therefore, although the present investigation allowed for identification of areas within the MTL specifically contributing to retrieval success by dissociating them from those also contributing to incidental encoding success during retrieval, the latter findings should be treated with caution. A high degree of specificity within the MTL in the current study is also limited due to data acquisition and processing parameters. Anatomical specificity is impeded when examining small areas of neural tissue using 4 mm isotropic voxels for data acquisition along with normalization and smoothing kernel of 8 mm for data processing, although these parameters are not unusual for fMRI studies. Future studies using higher spatial resolution and minimal preprocessing will allow for more precise specificity when examining this issue in the MTL. Another limitation of the current study is the difference in delay between encoding and retrieval for EM-1 and EM-2. In EM-1 there were approximately 40 min separating the encoding and retrieval of an item, whereas in EM-2 there was approximately 1 week separating encoding and retrieval. This difference in delay could have resulted in a shift in retrieval processes that were used during the memory tasks (e.g., from recollection-based for EM-1 to familiarity-based for EM-2). Thus, it is possible that the current findings could be influenced by differences in the retrieval processes implemented across the two memory retrieval tasks. On the other hand, previous research suggests that recollection-based retrieval processes are associated with the highest LOC (Daselaar et al., 2006). Since we selected only trials with the highest LOC ratings for analysis in both memory tasks there is increased likelihood that memory for these trials is recollection-based in both memory tasks. Moreover, extant research on emotional memory shows that the enhancing effect of emotion results from recollection rather than familiarity-based memory processes (Dolcos et al., 2005; Dew et al., 2014). Examination of the relationship between the engagement of certain retrieval mechanisms for items tested during retrieval (e.g., recollection and familiarity) and those engaged for items incidentally encoded during retrieval, linked to the retention interval, is an open question for future research.

CONCLUSIONS

In summary, the present study yielded two novel findings pertaining to the neural mechanisms of emotional memory retrieval. First, the study distinguished between MTL retrieval and incidental encoding success activity linked to the memory-enhancing effect of emotion during retrieval. Greater emotional retrieval success was identified bilaterally in AMY, HC, and PHC. However, AMY activity was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success activity were largely uninvolved in encoding success. This finding demonstrates that MTL activity during retrieval can be dissociated and linked to different memory operations that occur during recognition memory. Second, MTL sub-regions were identified as showing different temporal and spatial dissociations in the BOLD response for the memory enhancement of emotional items vs. increased engagement associated with the memory for neutral items. An earlier and more anteriorly spread response (in left AMY and bilateral HC and PHC) was linked to greater emotional retrieval success, whereas a later and more posteriorly localized response (in right posterior PHC) was linked to greater engagement for neutral retrieval success. Taken together, these results shed light on the neural mechanisms of emotional memory retrieval in healthy behavior and are important for understanding maladaptive alterations in the processes subserving emotional memory found in populations with affective disorders (Whalley et al., 2009; Hayes et al., 2011; Dolcos, 2013).

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REFERENCES

Anderson, A. K., Yamaguchi, Y., Grabski, W., and Lacka, D. (2006). Emotional memories are not all created equal: evidence for selective memory enhancement. *Learn. Mem.* 13, 711–718. doi: 10.1101/lm.388906

Bannerman, R. L., Hibbard, P. B., Chalmers, K., and Sahraie, A. (2012). Saccadic latency is modulated by emotional content of spatially filtered face stimuli. *Emotion* 12, 1384–1392. doi: 10.1037/a0028677

Bannerman, R. L., Milders, M., de Gelder, B., and Sahraie, A. (2009). Orienting to threat: faster localization of fearful facial expressions and body postures revealed by saccadic eye movements. *Proc. Biol. Sci.* 276, 1635–1641. doi: 10.1098/rspb.2008.1744

Bradley, M. M., Greenwald, M. K., Petry, M. C., and Lang, P. J. (1992). Remembering pictures: pleasure and arousal in memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 18, 379–390. doi: 10.1037/0278-7393.18.2.379

Chiu, Y. C., Dolcos, F., Gonsalves, B. D., and Cohen, N. J. (2013). On opposing effects of emotion on contextual or relational memory. *Front. Psychol.* 4:103. doi: 10.3389/fpsyg.2013.00103

Christianson, S. A. (1992). Emotional stress and eyewitness memory: a critical review. *Psychol. Bull.* 112, 284–309. doi: 10.1037/0033-2909.112.2.284

Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J. Neurophysiol.* 96, 1902–1911. doi: 10.1152/jn.01029.2005

Daselaar, S. M., Rice, H. J., Greenberg, D. L., Cabeza, R., LaBar, K. S., and Rubin, D. C. (2008). The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. *Cereb. Cortex* 18, 217–229. doi: 10.1093/cercor/bhm048

Dew, I. T. Z., Ritchey, M., LaBar, K. S., and Cabeza, R. (2014). Prior perceptual processing enhances the effect of emotional arousal on the neural correlates of memory retrieval. *Neurobiol. Learn. Mem.* doi: 10.1016/j.nlm.2013.12.012. [Epub ahead of print].

Dolcos, F. (2013). Linking enhancing and impairing effects of emotion-the case of PTSD. *Front. Integr. Neurosci.* 7:26. doi: 10.3389/fnint.2013.00026

Dolcos, F., and Cabeza, R. (2002). Event-related potentials of emotional memory: encoding pleasant, unpleasant, and neutral pictures. *Cogn. Affect. Behav. Neurosci.* 2, 252–263. doi: 10.3758/CABN.2.3.252

Dolcos, F., and Denkova, E. (2008). Neural correlates of encoding emotional memories: a review of functional neuroimaging evidence. *Cell Sci. Rev.* 5, 78–122.

Dolcos, F., Denkova, E., and Dolcos, S. (2012). Neural correlates of emotional memories: a review of evidence from brain imaging studies. *Psychologica* 55, 80–111. doi: 10.2117/psysoc.2012.80

Dolcos, F., Diaz-Granados, P., Wang, L., and McCarthy, G. (2008). Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. *Neuropsychologia* 46, 326–335. doi: 10.1016/j.neuropsychologia.2007.07.010

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 42, 855–863. doi: 10.1016/S0896-6273(04)00289-2

Dolcos, F., LaBar, K. S., and Cabeza, R. (2005). Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proc. Natl. Acad. Sci. U.S.A.* 102, 2626–2631. doi: 10.1073/pnas.0409848102

Dolcos, F., and McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *J. Neurosci.* 26, 2072–2079. doi: 10.1523/JNEUROSCI.5042-05.2006

Dougal, S., Phelps, E. A., and Davachi, L. (2007). The role of medial temporal lobe in item recognition and source recollection of emotional stimuli. *Cogn. Affect. Behav. Neurosci.* 7, 233–242. doi: 10.3758/CABN.7.3.233

Genovese, C. R., Lazar, N. A., and Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15, 870–878. doi: 10.1006/nimg.2001.1037

Hayes, J. P., LaBar, K. S., McCarthy, G., Selgrade, E., Nasser, J., Dolcos, F., et al. (2011). Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. *J. Psychiatr. Res.* 45, 660–669. doi: 10.1016/j.jpsychires.2010.10.007

Huettel, S. A., and McCarthy, G. (2001). The effects of single-trial averaging upon the spatial extent of fMRI activation. *Neuroreport* 12, 2411–2416. doi: 10.1097/00001756-200108080-00025

Johnson, J. D., McDuff, S. G., Rugg, M. D., and Norman, K. A. (2009). Recollection, familiarity, and cortical reinstatement: a multivoxel pattern analysis. *Neuron* 63, 697–708. doi: 10.1016/j.neuron.2009.08.011

Johnson, J. D., and Rugg, M. D. (2007). Recollection and the reinstatement of encoding-related cortical activity. *Cereb. Cortex* 17, 2507–2515. doi: 10.1093/cercor/bhl156

Kensinger, E. A., and Schacter, D. L. (2005). Retrieving accurate and distorted memories: neuroimaging evidence for effects of emotion. *Neuroimage* 27, 167–177. doi: 10.1016/j.neuroimage.2005.03.038

Kleinsmith, L. J., and Kaplan, S. (1963). Paired-associate learning as a function of arousal and interpolated interval. *J. Exp. Psychol.* 65:3. doi: 10.1037/h0040288

Kroes, M. C., Strange, B. A., and Dolan, R. J. (2010). Beta-adrenergic blockade during memory retrieval in humans evokes a sustained reduction of declarative emotional memory enhancement. *J. Neurosci.* 30, 3959–3963. doi: 10.1523/JNEUROSCI.5469-09.2010

LaBar, K. S., and Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* 7, 54–64. doi: 10.1038/nrn1825

Lang, P. J., Bradley, M. M., and Cuthbert, B. N. (2008). *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-8.* Gainsville, FL: Center for the Study of Emotion and Attention at the University of Florida.

Larson, C. L., Schaefer, H. S., Siegle, G. J., Jackson, C. A., Anderle, M. J., and Davidson, R. J. (2006). Fear is fast in phobic individuals: amygdala activation in response to fear-relevant stimuli. *Biol. Psychiatry* 60, 410–417. doi: 10.1016/j.biopsych.2006.03.079

Lieberman, M. D., and Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc. Cogn. Affect. Neurosci.* 4, 423–428. doi: 10.1093/scan/nsp052

Macmillan, N. A., and Creelman, C. D. (1991). *Detection Theory: a User's Guide.* New York, NY: Cambridge University Press.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* 27, 1–28. doi: 10.1146/annurev.neuro.27.070203.144157

Mendez-Bertolo, C., Moratti, S., Toledano, R., Martinez-Alvarez, R., Mah, Y. H., Gil-Nagel, A., et al. (2013). "High and low road for fear perception in humans," in *Paper presented at the Program Number 184.07. 2013 Neuroscience Meeting Planner,* (San Diego, CA: Society for Neuroscience, 2013).

Moore, M., Hu, Y., Woo, S., O'Hearn, D., Iordan, A. D., Dolcos, S., et al. (2014). A comprehensive protocol for manual segmentation of the medial temporal lobe structures. *J. Vis. Exp.* (accepted).

Morey, R. A., Dolcos, F., Petty, C. M., Cooper, D. A., Hayes, J. P., LaBar, K. S., et al. (2009). The role of trauma-related distractors on neural systems for working memory and emotion processing in posttraumatic stress disorder. *J. Psychiatr. Res.* 43, 809–817. doi: 10.1016/j.jpsychires.2008.10.014

Murty, V. P., Ritchey, M., Adcock, R. A., and LaBar, K. S. (2011). Reprint of: fMRI studies of successful emotional memory encoding: a quantitative meta-analysis. *Neuropsychologia* 49, 695–705. doi: 10.1016/j.neuropsychologia.2011.02.031

Nader, K., and Einarsson, E. O. (2010). Memory reconsolidation: an update. *Ann. N.Y. Acad. Sci.* 1191, 27–41. doi: 10.1111/j.1749-6632.2010.05443.x

Nichols, T., Brett, M., Andersson, J., Wager, T., and Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage* 25, 653–660. doi: 10.1016/j.neuroimage.2004.12.005

Nyberg, L., Habib, R., McIntosh, A. R., and Tulving, E. (2000). Reactivation of encoding-related brain activity during memory retrieval. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11120–11124. doi: 10.1073/pnas.97.20.11120

Olofsson, J. K., Nordin, S., Sequeira, H., and Polich, J. (2008). Affective picture processing: an integrative review of ERP findings. *Biol. Psychol.* 77, 247–265. doi: 10.1016/j.biopsycho.2007.11.006

Ritchey, M. (2008). Renal sparing surgery for children with bilateral Wilms tumor. *Cancer* 112, 1877–1878. doi: 10.1002/cncr.23387

Ritchey, M., Dolcos, F., and Cabeza, R. (2008). Role of amygdala connectivity in the persistence of emotional memories over time: an event-related FMRI investigation. *Cereb. Cortex* 18, 2494–2504. doi: 10.1093/cercor/bhm262

Ritchey, M., LaBar, K. S., and Cabeza, R. (2011). Level of processing modulates the neural correlates of emotional memory formation. *J. Cogn. Neurosci.* 23, 757–771. doi: 10.1162/jocn.2010.21487

Ritchey, M., Wing, E. A., Labar, K. S., and Cabeza, R. (2013). Neural similarity between encoding and retrieval is related to memory via hippocampal interactions. *Cereb. Cortex* 23, 2818–2828. doi: 10.1093/cercor/bhs258 bhs258

Schuyler, B. S., Kral, T. R., Jacquart, J., Burghy, C. A., Weng, H. Y., Perlman, D. M., et al. (2012). Temporal dynamics of emotional responding: amygdala recovery predicts emotional traits. *Soc. Cogn. Affect. Neurosci.* 9, 176–181. doi: 10.1093/scan/nss131nss131

Seidenbecher, T., Laxmi, T. R., Stork, O., and Pape, H. C. (2003). Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science* 301, 846–850. doi: 10.1126/science.1085818

Sergerie, K., Lepage, M., and Armony, J. L. (2006). A process-specific functional dissociation of the amygdala in emotional memory. *J. Cogn. Neurosci.* 18, 1359–1367. doi: 10.1162/jocn.2006.18.8.1359

Shafer, A. T., and Dolcos, F. (2012). Neural correlates of opposing effects of emotional distraction on perception and episodic memory: an event-related FMRI investigation. *Front. Integr. Neurosci.* 6:70. doi: 10.3389/fnint.2012.00070

Shafer, A. T., Matveychuk, D., Penney, T., O'Hare, A. J., Stokes, J., and Dolcos, F. (2012). Processing of emotional distraction is both automatic and modulated by attention: evidence from an event-related fMRI investigation. *J. Cogn. Neurosci.* 24, 1233–1252. doi: 10.1162/jocn_a_00206

Sharot, T., Delgado, M. R., and Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nat. Neurosci.* 7, 1376–1380. doi: 10.1038/nn1353

Sharot, T., and Phelps, E. A. (2004). How arousal modulates memory: disentangling the effects of attention and retention. *Cogn. Affect. Behav. Neurosci.* 4, 294–306. doi: 10.3758/CABN.4.3.294

Sharot, T., and Yonelinas, A. P. (2008). Differential time-dependent effects of emotion on recollective experience and memory for contextual information. *Cognition* 106, 538–547. doi: 10.1016/j.cognition.2007.03.002

Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., and Carter, C. S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol. Psychiatry* 51, 693–707. doi: 10.1016/S0006-3223(02)01314-8

Smith, A. P., Stephan, K. E., Rugg, M. D., and Dolan, R. J. (2006). Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron* 49, 631–638. doi: 10.1016/j.neuron.2005.12.025

Stark, C. E., and Okado, Y. (2003). Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *J. Neurosci.* 23, 6748–6753.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289. doi: 10.1006/nimg.2001.0978

Uncapher, M. R., and Rugg, M. D. (2005). Effects of divided attention on fMRI correlates of memory encoding. *J. Cogn. Neurosci.* 17, 1923–1935. doi: 10.1162/089892905775008616

Ungerleider, L. G. (1995). Functional brain imaging studies of cortical mechanisms for memory. *Science* 270, 769–775. doi: 10.1126/science.270.5237.769

Whalley, M. G., Rugg, M. D., Smith, A. P., Dolan, R. J., and Brewin, C. R. (2009). Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. *Brain Cogn.* 69, 98–107. doi: 10.1016/j.bandc.2008.05.008

Wheeler, M. E., Petersen, S. E., and Buckner, R. L. (2000). Memory's echo: vivid remembering reactivates sensory-specific cortex. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11125–11129. doi: 10.1073/pnas.97.20.11125

Yamasaki, H., LaBar, K. S., and McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. *Proc. Natl. Acad. Sci. U.S.A.* 99, 11447–11451. doi: 10.1073/pnas.182176499

Yonelinas, A. P. (2001). Components of episodic memory: the contribution of recollection and familiarity. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1363–1374. doi: 10.1098/rstb.2001.0939

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Emotional face expression modulates occipital-frontal effective connectivity during memory formation in a bottom-up fashion

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This study investigated the role of bottom-up and top-down neural mechanisms in the processing of emotional face expression during memory formation. Functional brain imaging data was acquired during incidental learning of positive ("happy"), neutral and negative ("angry" or "fearful") faces. Dynamic Causal Modeling (DCM) was applied on the functional magnetic resonance imaging (fMRI) data to characterize effective connectivity within a brain network involving face perception (inferior occipital gyrus and fusiform gyrus) and successful memory formation related areas (hippocampus, superior parietal lobule, amygdala, and orbitofrontal cortex). The bottom-up models assumed processing of emotional face expression along feed forward pathways to the orbitofrontal cortex. The top-down models assumed that the orbitofrontal cortex processed emotional valence and mediated connections to the hippocampus. A subsequent recognition memory test showed an effect of negative emotion on the response bias, but not on memory performance. Our DCM findings showed that the bottom-up model family of effective connectivity best explained the data across all subjects and specified that emotion affected most bottom-up connections to the orbitofrontal cortex, especially from the occipital visual cortex and superior parietal lobule. Of those pathways to the orbitofrontal cortex the connection from the inferior occipital gyrus correlated with memory performance independently of valence. We suggest that bottom-up neural mechanisms support effects of emotional face expression and memory formation in a parallel and partially overlapping fashion.

Keywords: Dynamic Causal Modeling, fMRI, facial affect, memory formation

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Introduction

It is well-established that emotional stimuli can enhance learning (Hamann, 2001; Roozendaal and McGaugh, 2011). This enhancement has been attributed to initial encoding (Murty et al., 2010), memory consolidation (McGaugh, 2004), and retrieval processes (Sharot et al., 2004; Dolcos et al., 2005). In addition to neural interactions between the amygdala and the medial temporal lobe

memory system playing a pivotal role in these processes (Dolcos et al., 2004b; LaBar and Cabeza, 2006; Smith et al., 2006; Ritchey et al., 2008), there is now increasing evidence for other neural regions contributing to the initial memory formation of emotional memories in a bottom-up and top-down manner (Dolcos et al., 2004a; Kensinger and Corkin, 2004; Mickley and Kensinger, 2008; Mather and Sutherland, 2011; Ritchey et al., 2011).

First of all, emotional stimuli can capture attention that facilitates participation of multiple regions during perception (Vuilleumier and Driver, 2007; Pessoa and Adolphs, 2010). Some of these pathways may initially bypass the amygdala and indirectly contribute to emotional memory (Kensinger and Corkin, 2004; Sergerie et al., 2005). For example, functional connectivity studies reported that emotional stimuli modulate neural activity along parallel forward pathways from visual regions to the frontal cortex, which suggests that emotional face expression facilitates perception in a bottom-up fashion. These studies do not support a mediating role of the amygdala in perception of emotional faces (Fairhall and Ishai, 2007; Dima et al., 2011). Secondly, the frontal cortex encompasses different regions that contribute to emotional memory (LaBar and Cabeza, 2006). For example, top-down connections from the orbitofrontal cortex, a region implicated in the representation of affective value, reward and behavioral guidance, have a pivotal role in emotion mediated learning (Rolls et al., 1994; Kumfor et al., 2013). Thus, while the amygdala plays a key role in rapid detection of facial affect through implicit processing (Hariri et al., 2003; Fitzgerald et al., 2006), the prefrontal cortex exerts semantic or elaborative processing via mechanisms of selective attention (Armony and Dolan, 2002). The orbitofrontal cortex not only modulates the connectivity between the amygdala and hippocampus during retrieval of emotional stimuli (Smith et al., 2006), but also constitutes a direct network with the hippocampus that mediates processing of positive emotional stimuli and increased feelings of familiarity (Mickley and Kensinger, 2008). Therefore, bottom-up activity to the orbitofrontal cortex and top-down elaborative processing of affective value in the orbitofrontal cortex on connections to the hippocampus might play important roles in the formation of emotional memories. It is however, unclear how multiple regions collaborate to support one of the two fashions and predict successful memory formation.

It should also be noted that the assumption of an automatic memory enhancement by emotional stimuli may be too simple (Bennion et al., 2013). Emotional stimuli can enhance both recall accuracy and subjective feelings of recollection (Phelps and Sharot, 2008). In conditions exerting low distinctiveness (and high inter-item relatedness) between old and new items, it was often observed that an elevation of the number of correctly identified old items was accompanied by an increase in the number of incorrect identifications of new or related items (i.e., false alarms/false memories), which means that emotional stimuli can change the response bias without improving memory performance (Dougal and Rotello, 2007; Brainerd et al., 2008).This emotion-induced recognition bias might reflect flexible criterion setting triggered by emotional valence that works to ensure that emotional stimuli are not missed or considered irrelevant (Windmann and Kutas, 2001). The emotion-induced recognition bias is less evident during conscious retrieval than during familiarity-based recognition operations (Ochsner, 2000; Johansson et al., 2004), suggesting that top-down processes play a role in rejecting emotion induced false memories. More so, for stimuli with positive affect the role of top-down processing in memory may be even more important as memories of positive stimuli depend more on gist and attention-related mechanisms (Talmi et al., 2007, 2008; Mickley and Kensinger, 2008; Mickley Steinmetz and Kensinger, 2009). Hence, when studying neural mechanisms of emotional memory, we need to take into account that emotionally valenced stimuli can influence both memory performance and response bias.

The present study utilized Dynamic Causal Modeling (DCM) of functional magnetic resonance imaging (fMRI) (Friston et al., 2003) in an incidental learning task of faces with positive ("happy"), neutral and negative ("angry" or "fearful") emotional expressions. Our first aim was to evaluate whether bottom-up or top-down models best explain variations in neural activity during memory formation of emotional faces. Effective neural networks were characterized to elucidate the effect of emotional face expression on memory formation. In bottom-up models we hypothesized that faces with emotional expressions would engage neural pathways in a bottom-up manner to the frontal cortex (Kensinger and Corkin, 2004; Talmi et al., 2008; Dima et al., 2011). In top-down models the frontal cortex would receive stimuli with positive and negative expressions and then modulate connections to the hippocampus (Sergerie et al., 2005; Smith et al., 2006; Mickley Steinmetz and Kensinger, 2009; Ritchey et al., 2011). The best fitting model across subjects was selected and connectivity strengths were utilized to predict memory performance and response bias. Since bottom-up processes are important in perception of emotional faces (Fairhall and Ishai, 2007; Dima et al., 2011) and episodic memory formation (Dickerson et al., 2007; Sepulcre et al., 2008), we expect that the bottom-up model best explains memory formation of emotional faces. Our second aim was to examine whether pathways involved in emotional face processing directly contribute to memory performance. Based on the role of frontal and visual areas in memory formation and emotional face processing, we expect that pathways between these areas are involved in both these processes.

Method

Eighteen healthy male adults (age 18–35 years old, mean = 27.6 years, $SD = 5.1$) without psychiatric or neurological disorders were recruited through advertisement at the university campus (University of Zurich). All subjects were German speakers, with 33.3% Swiss German speakers. They provided written informed consent and received payment for their participation. The study was in accordance with the guidelines of the local ethics review board of the Canton of Zurich.

Experimental Procedure

This study investigated the influence of face expression (negative, positive, and neutral) on memory formation in an incidental-learning paradigm. Ratings on emotional valence and attractiveness were used to select the most and least attractive

pictures respectively for both male and female faces with positive ("happy"), negative ("angry") and neutral expressions (Rimmele et al., 2009; Dinkelacker et al., 2011) (examples are shown in **Figure 1**). The pictures of faces were an assembly from different databases: NimStim Face Stimulus set (www.macbrain.org), Karolinska Directed Emotional Faces database (KDEF; www.emotionlab.se/resources/kdef) and freely available photographers pictures (www.photo.net). These were formatted to a uniform standard grayscale pictures of adult faces with direct eye contact, cut in an ellipsoid shape on a black background. Hair, glasses, beard were allowed, but approximately equally distributed across emotional valence (Dinkelacker et al., 2011). The negative faces had angry and fearful expressions, the positive faces had happy expressions. These pictures were rated independently on a nine-point Likert scale and classified according to the valence rating ($n = 30$) in a previous study (Dinkelacker et al., 2011). The same set was also used and rated independently by Rimmele et al. (2009). This resulted in 148 faces. We added a small number of faces (20) from the Radboud Face Database with negative valence after formatting them into the same uniform standard. That database is a set of validated faces for positive, neutral and negative emotional expressions (Langner et al., 2010). Thus, the reported studies that validated these stimuli showed that on average there is a clear distinction between the valence of faces within the categories of face expression (positive, negative, and neutral). In three separate fMRI runs, subjects were presented with randomly intermixed 112 gray-scale faces of different attractiveness, valence, and gender. Each face was displayed for 3.5 s in the center of the screen. Inter-stimulus intervals varied between 2 and 18 s during which a fixation cross was shown. The tasks of the subjects was to judge "how much would you like to approach this person, if you encountered this person on the road?" and rank this judgment on a six-point scale (from "very willingly" to "very reluctantly"). For half of the subjects the buttons were ranked "1, 2, 3" for the left and "4, 5, 6" for the right hand. To minimize left/right side effects, the other half of the subjects used a reversed ranking order. Subjects were instructed to think well before deciding and to press the button when the fixation cross appeared. Subjects were not informed that this task would be followed by a memory test (Grady et al., 2002). Forty minutes after the study phase subjects completed a surprise recognition memory test outside the scanner in which 112 studies faces were intermixed with 56 new faces. For each face subjects were required to indicate by button press whether it was old or new on a six-point confidence scale (two response pads each with three buttons each ranging from "sure old" to "sure new").

Behavioral Analysis

This study only included the behavioral reactions to old and new faces without considering confidence level. We tested if confidence predicted memory performance or response bias, but found no significant interaction between confidence level and emotion on memory performance or response bias [$F_{(4,48)} < 1$, $p > 0.4$]. This justified collapsing across confidence levels and allowed us to increase statistical power. Specifically, hit rate denoted the correct recognition proportion of studied faces for which subjects reported "sure old," "rather old," or "unsure old." False alarm rate denoted the proportion of unstudied faces for which subjects incorrectly responded "sure old," "rather old," or "unsure old." Hit rate and false alarm rate were calculated for each face expression separately. Faces that did not yield a response were excluded from the analysis. Memory performance [Pr = p(hit rate – false alarm rate)] and response bias [Br = p[false alarm rate/[1 – (hit rate – false alarm rate)]]] were assessed according to the two-high-threshold theory (Snodgrass and Corwin, 1988). These scores were separately calculated for faces with positive, negative and neutral expressions. Statistical analysis on behavioral data relied on a repeated measures ANOVA with face expression as factor (positive, neutral, negative). Greenhouse–Geisser corrections were applied on degrees of freedom whenever sphericity assumptions were violated. All statistical analyses were performed using SPSS 19.

Brain Imaging Acquisition

Magnetic resonance imaging data were acquired on a General Electric Signa Excite 3.0 T whole-body scanner at the Center for MR Research of the University Children's Hospital Zurich. For fMRI three series of 159 scans sensitive to BOLD contrast

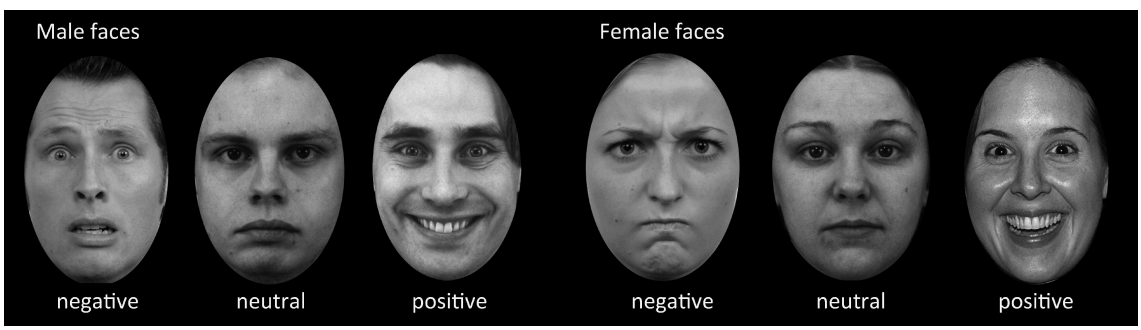


FIGURE 1 | Example stimuli used in the incidental-learning paradigm and recognition memory test. In the learning phase, the subjects were asked to judge "how much would you like to approach this person, if you encountered this person on the road?" on a six-point scale. The example pictures are adapted from different databases such as the NimStim Face Stimulus set, Karolinska Directed Emotional Faces Database, and Radboud Faces Database.

with 44 axial slices covering the whole brain were acquired with a T2*-sensitive multi-slice echo planar imaging (EPI) sequence (repetition time = 2.4 s; echo time = 32 ms; field of view = 240 cm; image matrix = 64 × 64; voxel size = 3.75 × 3.75 × 3.50 mm^3; flip angle = 80°). The first four scans were discarded to allow for equilibration effects. Other scans were acquired that are beyond the scope of this paper.

fMRI Analysis

Preprocessing

Data were analyzed using SPM12b (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). All volumes were slice time corrected, realigned to the first volume, corrected for motion artifacts using the ArtRepair-toolbox that detected and corrected volumes for which the signal deviated more than three standard deviations or 1 mm movement per TR (Mazaika et al., 2007), normalized into standard stereotactic space using MNI template and smoothed with a 9 mm full-width at half maximum Gaussian kernel.

First Level Analysis

For each subject, we concatenated the data from three sessions and constructed a general linear model according to the emotional valences, where vector onsets represented negative, positive, and neutral face expressions. This model was used for the DCM analysis. In addition, a separate general linear model was modeled to define volumes of interest (VOIs). This model evaluated the subsequent memory effects and was based on the recognition test. Vector onsets represented remembered faces (participants pressed "sure old," "rather old," or "unsure old" on old items) and forgotten faces (participants pressed "sure new," "rather new," or "unsure new" on old items). The subsequent memory effect was identified from the contrast "remembered faces minus forgotten faces," and the face perception effect with all facial stimuli was identified by activity to both remembered and forgotten faces compared with baseline. Faces that yielded no responses during the recognition memory test entered the model as a regressor of no interest. All onsets of two models were convolved with a hemodynamic response function and a high-pass filter (128 s) was applied to remove low-frequency noise. Outlier parameters from the realignment procedure of the artifact-repaired data were used as covariates in the design matrix.

Volumes of Interest

We selected priori regions of interest at the second level. Random-effects analyses of the single-subject contrast images for the subsequent memory effect model were used to identify regions related to face perception (family-wise correction $p < 0.05$) and successful memory formation (subsequent memory effect: $p < 0.001$, uncorrected) at the group level. Due to the robust effect in left hippocampus, we limited our regions of interest to the left hemisphere, which was also motivated by Smith et al. (2006). As a result, face perception related regions included the inferior occipital gyrus (IOG: $x = -40$, $y = -78$, $z = -10$) and fusiform gyrus (FUS: $x = -36$, $y = -52$, $z = -10$). A subsequent memory effect was found in several limbic and non-limbic regions (**Table 1**). We restricted the DCM analysis to two limbic areas [hippocampus (HPC): $x = -30$, $y = -18$, $z = -14$ and amygdala (AMG): $x = -26$, $y = 2$, $z = -24$], and two non-limbic areas related to attention and emotion processing [superior parietal lobule (SPL): $x = -14$, $y = -68$, $z = 66$ and orbital frontal cortex (OFC): $x = 0$, $y = 62$, $z = -18$]. The HPC, AMG, and OFC were expected. We included the SPL, because this region was considered to be involved in visual-spatial attention and may support both memory and emotion. For each subject, six VOIs used for the DCM analysis were defined as 4 mm spheres at the center of the nearest local maximum of group maximum, within the same anatomical area (information about centers of VOI for each subject in Supplementary Table A). The time series of each VOIs were extracted by using Eigen variates of SPM12b separately using the emotion model.

Dynamic Causal Modeling

Model Specification

DCM identifies dynamic and non-linear systems in the brain that capture dependencies of brain regions over time and also considers their interactions between inputs and neural activity (Friston et al., 2003). We used the emotion model in order to clarify the emotional effects on connectivities. Assuming that

TABLE 1 | Brain regions related to successful memory formation based on the contrast between studied faces subsequently correctly recognized as old (hits) > studied faces subsequently identified as new (misses).

Region (AAL)	Lobe	L/R	Peak coordinates			Cluster size	*T*-values	Extend threshold (FDR)
			x	*y*	*z*			
Parahippocampal g.	Limbic	L	−18	−26	−20	47	4.23	0.09*
Parahippocampal g./amygdala	Limbic	R	22	2	−24	87	5.34	
Amygdala (AMG)	Limbic	L	−26	2	−24	13	4.88	
Hippocampus (HPC)	Limbic	L	−30	−18	−14	12	4.31	
Posterior cingulate g.	Limbic	R	4	−44	6	153	4.81	0.025
Superior parietal lobule (SPL)/precuneus	Parietal	L	−14	−68	66	148	5.77	0.025
Orbital frontal cortex (OFC)/rectus g.	Frontal	R/L	0	62	−18	111	5.53	0.053*
Cerebellum 9/medulla	Cerebellum	R/L	8	−40	−52	282	6.14	0.003

Results are reported at a height threshold of $p < 0.001$, uncorrected. Areas outside the limbic lobe are reported only when they survived or showed a trend (*) after cluster extent correction (FDR $p < 0.05$). Regions are listed based on the largest AAL cluster according to the xjview toolbox. Abbreviations: g, gyrus.

emotional valence mediated propagation of face processing during encoding, an initial model for all subjects included bidirectional endogenous connections between all six regions and a main effect of "all faces" as the driving input entering the visual region, IOG. According to our hypotheses, this model was differentiated into bottom-up (BU) and top-down (TD) family models (**Figure 4A**). BU family models indicate that emotion (negative and positive valences) modulated parallel forward pathways to the OFC during encoding. Emotion can influence one or more pathways from the IOG, FUS, SPL, HPC, and AMG to the OFC, which contributed to 27 bilinear models. TD family models depicted that emotion influenced the modulatory effect of the OFC on one or more connections with the hippocampus. That is, the emotional stimuli (positive and negative faces) were directly processed in the OFC. The OFC then modulated one or multiple connections from the IOG, FUS, SPL, and AMG to the HPC. The TD model family consisted of 15 non-linear models. Details about model specification are shown in Supplementary Table B. To sum up, we produced 42 variants of DCM models with 30 endogenous connections representing the functional coupling between each of the six regions. Modulatory effects consisted of five emotional effects in the bottom-up family (facial affect on connections from IOG, FUS, SPL, HPC, and AMG to OFC) and four effects of the OFC in the top-down family (the modulation from OFC on the connections from IOG, FUS, SPL, and AMG to HPC).

Model Comparison

DCM can utilize family level inference and Bayesian model averaging (BMA) to select the model families and estimate the effective connectivities of optimal model(s) within families (Friston et al., 2003; Penny et al., 2010). Crucially, family inferences allow a large number of models to compare and provide more than one model as overwhelming winner. Family comparison and model selection was implemented using random-effects (RFX) Bayesian model selection (BMS) in SPM12b (Stephan et al., 2009; Penny et al., 2010). Two indices, the expected and exceedance probabilities, which were computed from the posterior densities over 42 models, denoted the level of confidence with which a given model outperformed any other model tested. In family inferences, the winner was selected between the BU family and TD family. Family level posteriors are a summation of model level posteriors over family members. Furthermore, in order to investigate whether the effective connectivities supported the memory formation, we applied the random effects of BMA to acquire subjects' connectivity estimates across all models based on the group winning family (Penny et al., 2010). We then used Spearman correlations to evaluate associations between behavioral measures (memory performance and response bias) and parameters for endogenous connections and modulatory effects of emotion on connections in the winning family. Since we were interested only in the connections that were relevant for emotion processing we tested only those endogenous connections and modulatory connections in the winning family that connect to the OFC in the BU model family, respectively to the HPC in the TD model family and applied Bonferroni correction accordingly.

Results

Behavioral Results

For the behavioral analysis we calculated effects of emotion on memory performance for each expression separately (Pr = HR − FR) and response bias (Br = FR/(1 − (HR-FR)) (HR, hit rate, FR, false alarm rate). Memory performance and response bias for total and for each emotional face expression separately were significantly larger than 0 (all $p < 0.05$). A repeated measures ANOVA showed no effect of face expression on memory performance [$F_{(2,34)} = 1.05$, $p = 0.36$, $\eta^2 = 0.058$], but response bias was significantly different between emotional faces [$F_{(2,\ 34)} = 6.13$, $p = 0.005$, $\eta^2 = 0.265$]. The response bias was higher for negative faces than neutral [$t_{(17)} = 2.18$, $p = 0.044$, effect size $r = 0.323$] and positive faces [$t_{(17)} = 3.13$, $p = 0.006$, effect size $r = 0.379$] (**Figure 2**).

Subsequent Memory Effect

Within our neuroimaging data we found a subsequent memory effect in several limbic and non-limbic areas. Limbic areas

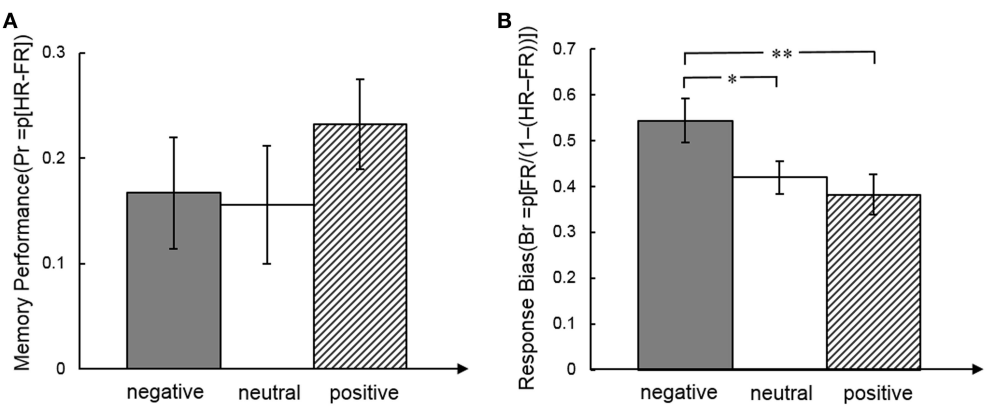


FIGURE 2 | Memory performance (A) and response bias (B) measures for emotional face expression. *Post-hoc t*-tests indicated differences between emotional face expressions. *$p < .05$; **$p < .01$.

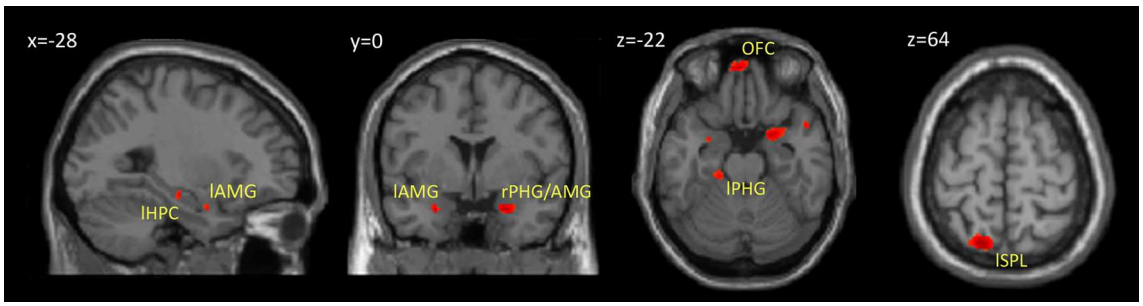


FIGURE 3 | Brain regions showing a subsequent memory effect. The figure shows the results from contrast between subsequently recognized faces (hits) and subsequently forgotten faces (misses) ($p < 0.001$, uncorrected). Abbreviations are listed in **Table 1**.

included the left hippocampus, bilateral amygdalae, left parahippocampal gyrus, and posterior cingulate gyrus. Activity outside the limbic cortex was found in the posterior cerebellum, left superior parietal lobule, and medial frontal cortex including the rectus gyrus and orbital frontal gyrus. Details are provided in **Table 1** and **Figure 3**.

Family Comparison and Model Selection

First we executed the family comparison between bottom-up models family (totally 27 models) and top-down models family (totally 15 models). The BU family models were superior to the TD family with an exceedance probability of 99.3% across all subjects (**Figure 4B**). Comparing the individual 42 models, Model 25 with the highest exceedance probability of 48.1% indicated that emotion affected all pathways to the OFC except the pathway from the FUS to the OFC (Model 25 in Supplementary Table B). The second-best model, Model 24, with 19.7% exceedance probability and Model 16 with 13.8% exceedance probability indicated that the connections from AMG and HPC to OFC received weaker affective effects than IOG and SPL to OFC (**Figure 4D**). We then used the random effects of BMA to acquire subjects' connectivity estimates for endogenous and modulatory parameters. **Figure 4C** shows the posterior densities of average network parameters from random effects BMA. Of the bottom-up pathways, the IOG, FUS, and HPC had positive endogenous connections to the OFC. Within them, IOG→OFC received negative modulations from both negative and positive emotional expressions (modulatory parameter for negative expression: Median = −0.096, 25% quartile = −0.499, 75% quartile = 0.583; for positive expressions: Median = −0.095, 25% quartile = −0.578, 75% quartile = 0.259). The connection SPL→OFC received negative modulations from positive emotional expressions (Median = −0.450, 25% quartile = −1.272, 75% quartile = −0.024). The modulatory parameter estimates were negative, which indicated that an enhancement of activity associated with facial affect in the IOG and SPL resulted in suppression of activity in the OFC.

Correlations between Connectivity Estimates and Behavior

Correlation analysis between the BMA estimates of BU endogenous connections and behavioral measures across all subjects revealed a significant negative correlation between memory performance and the IOG→OFC pathway ($r_s = -0.680$, $p = 0.002$). This correlation was found for faces with all emotional expressions (correlation with Pr-negative: $r_s = -0.523$, $p = 0.026$; Pr-neutral: $r_s = -0.598$, $p = 0.009$; Pr-positive: $r_s = -0.647$, $p = 0.004$; **Figure 5**) and survived Bonferroni correction ($\alpha < 0.0033$, see **Table 2**). This negative correlation indicated that neural activity in the IOG elicited an inhibition of activity in the OFC in high performers, whereas it yields a facilitation of activity in the OFC of low performers. We found no significant correlation between bottom-up endogenous parameters and response bias. As for the modulatory parameters, the effects of negative stimuli occurred in the correlations between connection SPL→OFC with response bias for negative faces ($r_s = 0.482$, $p = 0.043$) and connection AMG→OFC with total response bias ($r_s = 0.482$, $p = 0.043$). These correlations, however, did not survive Bonferroni correction.

Discussion

This study aimed at examining how emotional face expression is implemented in neural networks supporting memory formation of faces. We utilized DCM of fMRI to study effective connectivities during face encoding and compared "bottom-up" and "top-down" models that describe the influence of emotion on memory formation. In accordance with the theory that emotion operates during memory formation via multiple regions participating in perceptual, attentional, or semantic processes (LaBar and Cabeza, 2006), our DCM analysis was implemented in an extended network combining facial perception and memory formation related areas. Specifically, subsequently remembered faces were associated with higher activations compared to subsequently forgotten faces not only in limbic areas conveying the hippocampus, amygdala, and posterior cingulate gyrus, but also in the superior parietal lobe, orbitofrontal cortex and cerebellum. Whereas, limbic and orbitofrontal areas are frequently reported in the context of emotional memory operations, the superior parietal lobe and cerebellum are less often discussed. The superior parietal lobule is a region that can provide (spatial) attentional assistance during perception and memory processing (Hoffman and Haxby, 2000; Ciaramelli et al., 2008; Hutchinson et al., 2009; Uncapher and Rugg, 2009; von Allmen et al., 2013). The posterior

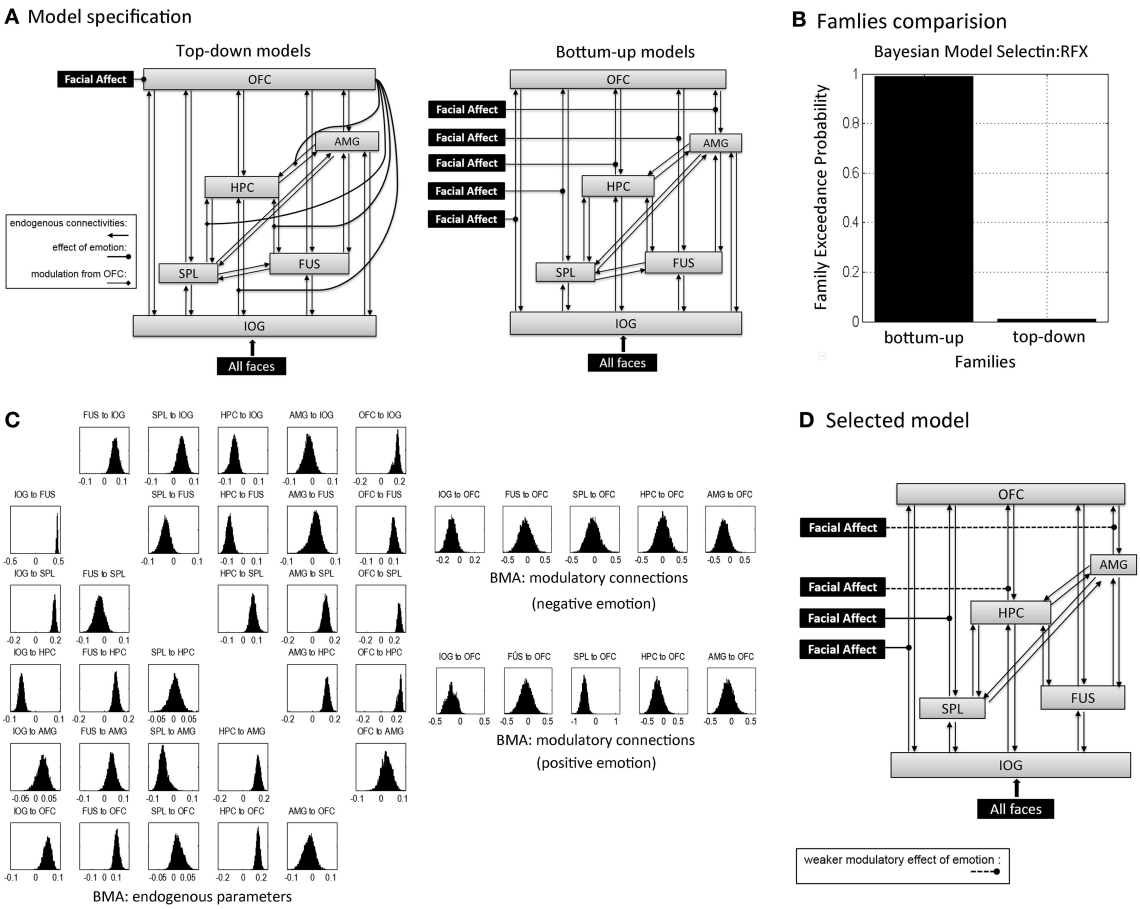


FIGURE 4 | Dynamic Causal Modeling analysis.(A) Concept models for the effective connectivity and emotional modulations within a memory-related network during learning in terms of the top-down and bottom-up approaches. Schematically, inputs of "all faces" are in visual region IOG; the modulations of facial affects correspond to negative and positive facial expressions. Model specification was based on these two concept models with one or several modulatory pathways (see in Supplementary Table B): each one of 27 bottom-up family models had one to five bottom-up pathways that received stimuli from affective faces; all 15 top-down family models processed affective faces in OFC, but each one of top-down models received one to four modulations from OFC. **(B)** The exceedance probability for family comparison based on random effects analysis from Dynamic Causal Modeling analysis. **(C)** The posterior densities of average network parameters from random effects Bayesian model averaging for endogenous connections (left) and modulatory connections for negative and positive emotional faces respectively (right). **(D)** The selected model by DCM analysis (model 25 in Supplementary Table B); the second and fourth best-fitting models implied weaker modulatory effects on the connections from the HPC and AMG to the OFC that are showed in dashed lines.

cerebellum has been also recognized in prospective cognitive and affective processing beyond strict motor planning (Schmahmann and Sherman, 1998; Cotterill, 2001; Chen et al., 2014).

The "bottom-up" model, in which emotion exerted effects along multiple parallel feed-forward pathways to the orbitofrontal cortex, prevailed across all subjects. This finding is in line with our hypothesis and suggests that emotion exerts parallel effects on multiple forward pathways to the prefrontal cortex (i.e., IOG→OFC, SPL→OFC, HPC→OFC, and AMG→OFC). The OFC has been associated with elaborative processing of valence and reward (O'Doherty et al., 2001; Kringelbach, 2005), which was tested in our top-down family models. However, the winning family of bottom-up models corresponds to the view that emotional stimuli are processed simultaneously along "many roads" across the face-processing network (Kensinger and Corkin, 2004; Pessoa and Adolphs, 2010). Furthermore, the results of model selection highlighted the effective connectivities from IOG and SPL to OFC, as these connections were present in all preferred models. Previous studies showed that the inferior fronto-occipital fascicle and superior longitudinal fascicle connect the visual system with the frontal cortex along dorsal and ventral pathways (Johnson et al., 1996; Martino et al., 2010; Sarubbo et al., 2013). The inferior connections build the ventral visual stream and engage functional coupling between visual and inferior prefrontal cortices supporting visual attention and perception (Gregoriou et al., 2009), while the superior connections extend upon the dorsal visual stream and connects to dorsal parts of the prefrontal cortex. The superior parietal lobe does not seem to have direct connections to the orbitofrontal cortex, but can provide attentional assistance for face perception

during gaze perception (Hoffman and Haxby, 2000), memory encoding (Uncapher and Rugg, 2005), retrieval (Ciaramelli et al., 2008), and working memory in alignment with hippocampal activity (Ranganath and D'Esposito, 2001; Nee and Jonides, 2013; von Allmen et al., 2013) and frontal regions (Olesen et al., 2003). The modulatory effect of emotion on the IOG-OFC and SPL-OFC connectivities in our task, might suggest that emotion modulates visual processes along the dorsal and ventral visual system during memory formation. The posterior densities of the modulatory BMA parameters tended to be negative, which would indicate that activity induced by emotionally valenced stimuli in the IOG resulted in suppression of activity in the OFC. Since modulatory BMA parameters were negative for positively and negatively valenced faces, it is possible that the OFC is actively suppressed by connecting regions as soon as emotional information is presented. This active suppression might prevent that emotional information does not distract from processing the facial features during the evaluation of approachability in the incidental learning task. It should be noted here, that modulation of the pathways to the OFC are independent from the intrinsic connections with the OFC.

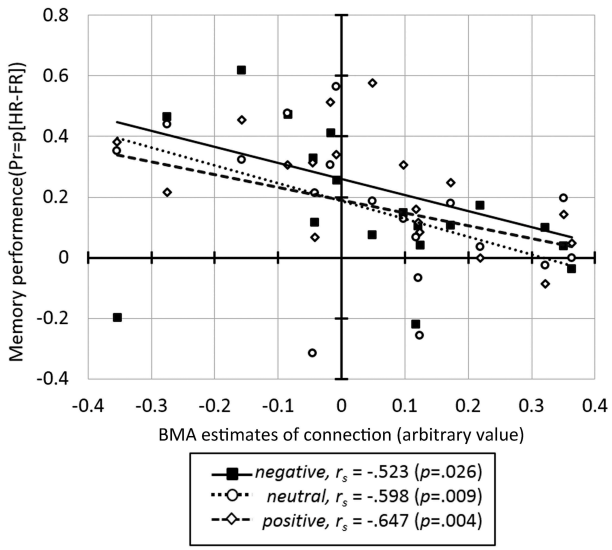


FIGURE 5 | The correlation between the BMA parameter estimates for the IOG→OFC connection and memory performance for faces in three emotional expressions.

Our second aim was to evaluate whether connectivities predict successful memory formation for emotionally valenced faces. Of all pathways to the OFC within the BU model we found that only the IOG to OFC endogenous connection negatively correlated with memory performance. All three expressions showed a similar correlation with endogenous connectivity. This means that for subjects with higher performance neural activity in the IOG caused a suppression of neural activity in the OFC, whereas in low performers activity in the IOG caused a facilitation of activity in the OFC. This mechanism was slightly more pronounced for positive face expressions, but there was no difference in correlation coefficients for the different emotional expressions. On average, there was a weak positive connectivity from the IOG to the OFC, as illustrated in **Figure 4C**, yet our results suggest that individual differences on the signal transfer between the IOG and OFC is associated with subsequent memory performance. One potential explanation for this effect might be that a higher decoupling between the visual processing areas and the frontal cortex is supportive during memory formation, because it may

TABLE 2 | Median and quartiles DCM endogenous parameters and modulatory estimates based on Bayesian model averaging (BMA) across all subjects and all models, and Spearman rho correlation (r_S) between parameters and behavioral performances.

	Median	Quartiles		Memory performance (r_S)				Response bias (r_S)			
		25%	75%	Total	Negative	Neutral	Positive	Total	Negative	Neutral	Positive
ENDOGENOUS PARAMETERS											
IOG→OFC	0.073	−0.055	0.184	−0.680**	−0.523*	−0.598**	−0.647**	0.026	0.228	−0.358	−0.098
FUS→OFC	0.047	−0.065	0.268	−0.067	0.018	−0.038	−0.131	0.280	−0.094	0.044	−0.333
SPL→OFC	0.047	−0.103	0.134	0.013	0.090	−0.079	0.036	0.034	−0.092	0.028	0.401
HPC→OFC	0.247	0.038	0.317	−0.201	−0.026	−0.174	−0.199	−0.255	−0.265	−0.011	0.015
AMG→OFC	−0.085	−0.145	0.175	−0.156	−0.119	0.038	−0.311	0.067	0.302	−0.230	0.234
MODULATORY ESTIMATES											
IOG→OFC, negative	−0.096	−0.499	0.583	0.321	−0.106	0.459	0.321	0.267	0.253	−0.040	−0.077
FUS→OFC, negative	−0.054	−0.342	0.109	0.267	0.232	0.046	0.451	−0.098	−0.373	−0.218	0.104
SPL→OFC, negative	0.038	−1.216	0.598	−0.207	−0.181	−0.042	−0.224	0.141	0.482*	0.300	0.094
HPC→OFC, negative	0.011	−0.277	0.534	0.011	0.121	−0.162	−0.003	−0.040	−0.317	−0.170	−0.129
AMG→OFC, negative	−0.442	−0.709	0.058	−0.152	−0.298	−0.133	−0.069	0.482*	0.284	0.162	0.280
IOG→OFC, positive	−0.095	−0.578	0.259	0.034	0.082	0.273	−0.358	−0.331	0.172	−0.422	−0.046
FUS→OFC, positive	−0.008	−0.270	0.266	0.222	0.038	0.311	0.015	−0.240	−0.290	−0.385	−0.331
SPL→OFC, positive	−0.450	−1.272	−0.024	0.022	0.112	0.119	−0.282	−0.185	0.187	−0.187	−0.437
HPC→OFC, positive	−0.027	−0.823	0.245	0.154	−0.059	0.131	0.278	0.185	−0.185	0.071	0.123
AMG→OFC, positive	−0.101	−0.564	0.166	−0.232	−0.063	−0.249	−0.166	0.309	0.247	0.007	−0.005

*$p < 0.05$; **$p < 0.0033$, *Bonferroni correction for multiple comparison (5 endogenous parameters and 10 modulatory parameters).*

prevent the frontal cortex from being overloaded during visual processing. Several studies reported increased functional coupling in resting state functional connectivity MRI between the hippocampus and the frontal cortex during and immediately after learning (Ranganath et al., 2005; Tambini et al., 2010), and between visual areas and the frontal cortex immediately after learning (Stevens et al., 2010). Few studies effectively investigated neural coupling during episodic memory formation, except for a few intracranial EEG studies that show coupling and decoupling between brain regions relevant for memory formation (Fell et al., 2001; Axmacher et al., 2008; Sehatpour et al., 2008). These studies suggested that sustained neural decoupling follows transient coupling between visual and hippocampal regions during successful memory formation. As far as we know such mechanisms have not yet been demonstrated between occipital and frontal regions. Yet, one might speculate that decoupling can follow transfer of information during coupling of neural networks. Such a mechanism might prevent that sensory information interferes with higher order processing of information. Thus, although evidence is still sparse, we tentatively suggest that the likelihood for memory formation to occur increases when the orbitofrontal cortex is temporary decoupled during evaluation of faces with different emotional expressions. Another point to note is that we found no differential effect of emotional valence on the association between connectivity and memory formation. It is important to remind, however, that we found no differential effect of emotional valence on memory performance either, so that inferences between emotional memory and connectivity cannot be drawn without further investigation. Taken together, model selection indicated that emotion modulated the IOG to OFC connection, while individual differences in memory performance were associated with endogenous connection strength, independently of emotional face expression. We thus suggest that the connectivity results tend to be in line with other views that emotion exerts parallel effects on perception (Calder and Young, 2005), attention and memory (Talmi et al., 2008, 2013).

DCM of fMRI provided an effective approach to investigate the effects of emotional face expression on memory formation. It should, however, be noted that combining and comparing Bayesian statistics with classical statistical approaches underlies limitations for interpretation of the data because DCM uses full time courses to estimate best fitting models, whereas correlations with connectivity estimates has much less statistical power. Nevertheless, we had a conservative classical statistical approach and sufficient statistical power to infer that connectivity estimates for the IOG→OFC were reliably related to memory performance. We also found that emotional face expression affected response bias, but not memory performance, which is in line with numerous recognition memory studies for emotional stimuli (Windmann and Kutas, 2001; Johansson et al., 2004; Dougal and Rotello, 2007; Brainerd et al., 2008). There is now some evidence that recognition memory operations might account for emotion induced differences in response bias at the behavioral and neural level. For example, emotion-induced recognition bias was associated with differences in frontal ERPs during recognition memory (Johansson et al., 2004). Similar to our study the authors reported no effect emotion induced enhancement of memory performance and only reported emotion induced enhancement of response bias at the behavioral level. Negative pictures also enhanced recollective experience, but not contextual detail of memory, and this recollective experience related to amygdala activity (Sharot et al., 2004). Enhanced focusing to specific details during recollection was also reported to induce recollective experience (Sharot et al., 2008). When negative faces induce enhanced focusing to a salient visual feature (i.e., the negative expression), independently of whether these items were new or old, this might elicit the phenomenon of recollective experience, even when a negative face is new. So all this evidence suggests that emotion induced response bias for negative faces relates to recognition operations rather than to memory formation processes that were studied here.

It should also be noted that the sample included healthy young male adults. Some studies included females and found that menstrual cycle influenced neural responses on emotional stimuli (Protopopescu et al., 2005). We chose to measure males to induce lower variance in the behavioral and neural data and to avoid variability in the data by factors we could not control for. It needs to be resolved whether our main results can be replicated in different samples, such as females, different age groups, or clinical samples for which similar networks were implicated (e.g., stress disorders, prosopagnosia) (Brewin et al., 2010; Dinkelacker et al., 2011). Moreover, our study investigated whether emotion contributed to the effective connectivity based on a network encompassing positive subsequent memory effects (remembered > forgotten). Whether emotion affects effective connectivities related to areas involved in forgetting (Daselaar et al., 2004) is another interesting topic that can be further investigated in future studies. Finally, our stimulus set included pictures of faces that had moderate valence. It is currently unclear if our main results hold under conditions of higher arousal induced by the stimuli, or by circumstantial information such as in real-world situations. Although several studies suggested that higher arousal captures attention and engages top-down elaborative processes (Dolcos et al., 2004a; Ritchey et al., 2011), it remains to be investigated whether such situations would also induce more top-down processing relative to bottom-up processing in effective connectivity. Taken together, we are confident to suggest that the pathways involved in modulating memory networks by emotion and pathways that successfully contribute to memory formation of emotional faces are partially overlapping and work in parallel in a bottom-up fashion.

Author Contributions

PK and MG conceptualized and designed the study; MG acquired the data; DX, MG, and PK analyzed the data; DX, PK wrote the paper.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnbeh.2015.00090/abstract

References

Armony, J. L., and Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia* 40, 817–826. doi: 10.1016/S0028-3932(01)00178-6

Axmacher, N., Schmitz, D. P., Wagner, T., Elger, C. E., and Fell, J. (2008). Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study. *J. Neurosci.* 28, 7304–7312. doi: 10.1523/JNEUROSCI.1778-08.2008

Bennion, K. A., Ford, J. H., Murray, B. D., and Kensinger, E. A. (2013). Oversimplification in the study of emotional memory. *J. Int. Neuropsychol. Soc.* 19, 953–961. doi: 10.1017/S1355617713000945

Brainerd, C., Stein, L., Silveira, R., Rohenkohl, G., and Reyna, V. (2008). How does negative emotion cause false memories? *Psychol. Sci.* 19, 919–925. doi: 10.1111/j.1467-9280.2008.02177.x

Brewin, C. R., Gregory, J. D., Lipton, M., and Burgess, N. (2010). Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. *Psychol. Rev.* 117, 210. doi: 10.1037/a0018113

Calder, A. J., and Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nat. Rev. Neurosci.* 6, 641–651. doi: 10.1038/nrn1724

Chen, S. H. A., Ho, M. H. R., and Desmond, J. E. (2014). A meta−analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Hum. Brain Mapp.* 35, 593–615. doi: 10.1002/hbm.22194

Ciaramelli, E., Grady, C. L., and Moscovitch, M. (2008). Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia* 46, 1828–1851. doi: 10.1016/j.neuropsychologia.2008.03.022

Cotterill, R. M. (2001). Cooperation of the basal ganglia, cerebellum, sensory cerebrum and hippocampus: possible implications for cognition, consciousness, intelligence and creativity. *Prog. Neurobiol.* 64, 1–33. doi: 10.1016/S0301-0082(00)00058-7

Daselaar, S., Prince, S., and Cabeza, R. (2004). When less means more: deactivations during encoding that predict subsequent memory. *Neuroimage* 23, 921–927. doi: 10.1016/j.neuroimage.2004.07.031

Dickerson, B. C., Miller, S. L., Greve, D. N., Dale, A. M., Albert, M. S., Schacter, D. L., et al. (2007). Prefrontal-hippocampal-fusiform activity during encoding predicts intraindividual differences in free recall ability: an event-related functional-anatomic MRI study. *Hippocampus* 17, 1060–1070. doi: 10.1002/hipo.20338

Dima, D., Stephan, K. E., Roiser, J. P., Friston, K. J., and Frangou, S. (2011). Effective connectivity during processing of facial affect: evidence for multiple parallel pathways. *J. Neurosci.* 31, 14378–14385. doi: 10.1523/JNEUROSCI.2400-11.2011

Dinkelacker, V., Grüter, M., Klaver, P., Grüter, T., Specht, K., Weis, S., et al. (2011). Congenital prosopagnosia: multistage anatomical and functional deficits in face processing circuitry. *J. Neurol.* 258, 770–782. doi: 10.1007/s00415-010-5828-5

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004a). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *Neuroimage* 23, 64–74. doi: 10.1016/j.neuroimage.2004.05.015

Dolcos, F., LaBar, K. S., and Cabeza, R. (2004b). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 42, 855–863. doi: 10.1016/S0896-6273(04)00289-2

Dolcos, F., LaBar, K. S., and Cabeza, R. (2005). Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proc. Natl. Acad. Sci. U.S.A.* 102, 2626–2631. doi: 10.1073/pnas.0409848102

Dougal, S., and Rotello, C. M. (2007). "Remembering" emotional words is based on response bias, not recollection. *Psychon. Bull. Rev.* 14, 423–429. doi: 10.3758/BF03194083

Fairhall, S. L., and Ishai, A. (2007). Effective connectivity within the distributed cortical network for face perception. *Cereb. cortex* 17, 2400–2406. doi: 10.1093/cercor/bhl148

Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C. E., et al. (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nat. Neurosci.* 4, 1259–1264. doi: 10.1038/nn759

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., and Phan, K. L. (2006). Beyond threat: amygdala reactivity across multiple expressions of facial affect. *Neuroimage* 30, 1441–1448. doi: 10.1016/j.neuroimage.2005.11.003

Friston, K. J., Harrison, L., and Penny, W. (2003). Dynamic causal modelling. *Neuroimage* 19, 1273–1302. doi: 10.1016/S1053-8119(03)00202-7

Grady, C. L., Bernstein, L. J., Beig, S., and Siegenthaler, A. L. (2002). The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. *Psychol. Aging* 17, 7–23. doi: 10.1037/0882-7974.17.1.7

Gregoriou, G. G., Gotts, S. J., Zhou, H., and Desimone, R. (2009). High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science* 324, 1207–1210. doi: 10.1126/science.1171402

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends Cogn. Sci.* 5, 394–400. doi: 10.1016/S1364-6613(00)01707-1

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., and Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biol. Psychiatry* 53, 494–501. doi: 10.1016/S0006-3223(02)01786-9

Hoffman, E. A., and Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nat. Neurosci.* 3, 80–84. doi: 10.1038/71152

Hutchinson, J. B., Uncapher, M. R., and Wagner, A. D. (2009). Posterior parietal cortex and episodic retrieval: convergent and divergent effects of attention and memory. *Learn. Mem.* 16, 343–356. doi: 10.1101/lm.919109

Johansson, M., Mecklinger, A., and Treese, A.-C. (2004). Recognition memory for emotional and neutral faces: An event-related potential study. *J. Cogn. Neurosci.* 16, 1840–1853. doi: 10.1162/0898929042947883

Johnson, P. B., Ferraina, S., Bianchi, L., and Caminiti, R. (1996). Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb. cortex* 6, 102–119. doi: 10.1093/cercor/6.2.102

Kensinger, E. A., and Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3310–3315. doi: 10.1073/pnas.0306408101

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 6, 691–702. doi: 10.1038/nrn1747

Kumfor, F., Irish, M., Hodges, J. R., and Piguet, O. (2013). The orbitofrontal cortex is involved in emotional enhancement of memory: evidence from the dementias. *Brain* 136, 2992–3003. doi: 10.1093/brain/awt185

LaBar, K. S., and Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* 7, 54–64. doi: 10.1038/nrn1825

Langner, O., Dotsch, R., Bijlstra, G., Wigboldus, D. H. J., Hawk, S. T., and Van Kippenberg, A. (2010). Presentation and validation of the Radboud Faces Database. *Cogn. Emot.* 24, 1377–1388. doi: 10.1080/02699930903485076

Martino, J., Brogna, C., Robles, S. G., Vergani, F., and Duffau, H. (2010). Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* 46, 691–699. doi: 10.1016/j.cortex.2009.07.015

Mather, M., and Sutherland, M. R. (2011). Arousal-biased competition in perception and memory. *Perspect. Psychol. Sci.* 6, 114–133. doi: 10.1177/1745691611400234

Mazaika, P., Whitfield-Gabrieli, S., Reiss, A., and Glover, G. (2007). "Artifact repair for fMRI data from high motion clinical subjects," in *13th Annual Meeting of the Organization for Human Brain Mapping* (Chicago, IL).

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* 27, 1–28. doi: 10.1146/annurev.neuro.27.070203.144157

Mickley, K. R., and Kensinger, E. A. (2008). Emotional valence influences the neural correlates associated with remembering and knowing. *Cogn. Affect. Behav. Neurosci.* 8, 143–152. doi: 10.3758/CABN.8.2.143

Mickley Steinmetz, K. R., and Kensinger, E. A. (2009). The effects of valence and arousal on the neural activity leading to subsequent memory. *Psychophysiology* 46, 1190–1199. doi: 10.1111/j.1469-8986.2009.00868.x

Murty, V. P., Ritchey, M., Adcock, R. A., and LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: a quantitative meta-analysis. *Neuropsychologia* 48, 3459–3469. doi: 10.1016/j.neuropsychologia.2010.07.030

Nee, D. E., and Jonides, J. (2013). Neural evidence for a 3-state model of visual short-term memory. *Neuroimage* 74, 1–11. doi: 10.1016/j.neuroimage.2013.02.019

Ochsner, K. N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J. Exp. Psychol. Gen.* 129:242. doi: 10.1037/0096-3445.129.2.242

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., and Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat. Neurosci.* 4, 95–102. doi: 10.1038/82959

Olesen, P. J., Nagy, Z., Westerberg, H., and Klingberg, T. (2003). Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cogn. Brain. Res.* 18, 48–57. doi: 10.1016/j.cogbrainres.2003.09.003

Penny, W. D., Stephan, K. E., Daunizeau, J., Rosa, M. J., Friston, K. J., Schofield, T. M., et al. (2010). Comparing families of dynamic causal models. *PLoS Comput. Biol.* 6:e1000709. doi: 10.1371/journal.pcbi.1000709

Pessoa, L., and Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat. Rev. Neurosci.* 11, 773–783. doi: 10.1038/nrn2920

Phelps, E. A., and Sharot, T. (2008). How (and Why) emotion enhances the subjective sense of recollection. *Curr. Dir. Psychol. Sci.* 17, 147–152. doi: 10.1111/j.1467-8721.2008.00565.x

Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., et al. (2005). Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proc. Natl. Acad. Sci. U.S.A.* 102, 16060–16065. doi: 10.1073/pnas.0502818102

Ranganath, C., and D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron* 31, 865–873. doi: 10.1016/S0896-6273(01)00411-1

Ranganath, C., Heller, A., Cohen, M. X., Brozinsky, C. J., and Rissman, J. (2005). Functional connectivity with the hippocampus during succesful memory formation. *Hippocampus* 15, 997–1005. doi: 10.1002/hipo.20141

Rimmele, U., Hediger, K., Heinrichs, M., and Klaver, P. (2009). Oxytocin makes a face in memory familiar. *J. Neurosci.* 29, 38–42. doi: 10.1523/JNEUROSCI.4260-08.2009

Ritchey, M., Dolcos, F., and Cabeza, R. (2008). Role of amygdala connectivity in the persistence of emotional memories over time: an event-related fMRI investigation. *Cereb. Cortex* 18, 2494–2504. doi: 10.1093/cercor/bhm262

Ritchey, M., LaBar, K. S., and Cabeza, R. (2011). Level of processing modulates the neural correlates of emotional memory formation. *J. Cogn. Neurosci.* 23, 757–771. doi: 10.1162/jocn.2010.21487

Rolls, E. T., Hornak, J., Wade, D., and McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J. Neurol. Neurosurg.* 57, 1518–1524. doi: 10.1136/jnnp.57.12.1518

Roozendaal, B., and McGaugh, J. L. (2011). Memory modulation. *Behav. Neurosci.* 125, 797. doi: 10.1037/a0026187

Sarubbo, S., De Benedictis, A., Maldonado, I. L., Basso, G., and Duffau, H. (2013). Frontal terminations for the inferior fronto-occipital fascicle: anatomical dissection, DTI study and functional considerations on a multi-component bundle. *Brain Struct. Func.* 218, 21–37. doi: 10.1007/s00429-011-0372-3

Schmahmann, J. D., and Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain* 121, 561–579. doi: 10.1093/brain/121.4.561

Sehatpour, P., Molholm, S., Schwartz, T. H., Mahoney, J. R., Mehta, A. D., Javitt, D. C., et al. (2008). A human intracranial study of long-range oscillatory coherence across a frontal-occipital-hippocampal brain network during visual object processing. *Proc. Natl. Acad. Sci U.S.A.* 105, 4399–4404. doi: 10.1073/pnas.0708418105

Sepulcre, J., Masdeu, J. C., Sastre-Garriga, J., Goñi, J., Vélez-de-Mendizábal, N., Duque, B., et al. (2008). Mapping the brain pathways of declarative verbal memory: Evidence from white matter lesions in the living human brain. *Neuroimage* 42, 1237–1243. doi: 10.1016/j.neuroimage.2008.05.038

Sergerie, K., Lepage, M., and Armony, J. L. (2005). A face to remember: emotional expression modulates prefrontal activity during memory formation. *Neuroimage* 24, 580–585. doi: 10.1016/j.neuroimage.2004.08.051

Sharot, T., Davidson, M. L., Carson, M. M., and Phelps, E. A. (2008). Eye movements predict recollective experience. *PLoS ONE* 3:e2884. doi: 10.1371/journal.pone.0002884

Sharot, T., Delgado, M. R., and Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nat. Neurosci.* 7, 1376–1380. doi: 10.1038/nn1353

Smith, A. P., Stephan, K. E., Rugg, M. D., and Dolan, R. J. (2006). Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron* 49, 631–638. doi: 10.1016/j.neuron.2005.12.025

Snodgrass, J. G., and Corwin, J. (1988). Pragmatics of Measuring recognition memory: applications to dementia and amnesia. *J. Exp. Psychol. Gen.* 117, 34–50. doi: 10.1037/0096-3445.117.1.34

Stephan, K. E., Penny, W. D., Daunizeau, J., Moran, R. J., and Friston, K. J. (2009). Bayesian model selection for group studies. *Neuroimage* 46, 1004–1017. doi: 10.1016/j.neuroimage.2009.03.025

Stevens, W. D., Buckner, R. L., and Schacter, D. L. (2010). Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. *Cereb. Cortex* 20, 1997–2006. doi: 10.1093/cercor/bhp270

Talmi, D., Anderson, A. K., Riggs, L., Caplan, J. B., and Moscovitch, M. (2008). Immediate memory consequences of the effect of emotion on attention to pictures. *Learn. Mem.* 15, 172–182. doi: 10.1101/lm.722908

Talmi, D., Schimmack, U., Paterson, T., and Moscovitch, M. (2007). The role of attention and relatedness in emotionally enhanced memory. *Emotion* 7, 89–102. doi: 10.1037/1528-3542.7.1.89

Talmi, D., Ziegler, M., Hawksworth, J., Lalani, S., Herman, C. P., and Moscovitch, M. (2013). Emotional stimuli exert parallel effects on attention and memory. *Cognit. Emot.* 27, 530–538. doi: 10.1080/02699931.2012.722527

Tambini, A., Ketz, N., and Davachi, L. (2010). Enhanced brain correlations during rest are related to memory for recent experiences. *Neuron* 65, 280–290. doi: 10.1016/j.neuron.2010.01.001

Uncapher, M. R., and Rugg, M. D. (2005). Effects of divided attention on fMRI correlates of memory encoding. *J. Cogn. Neurosci.* 17, 1923–1935. doi: 10.1162/089892905775008616

Uncapher, M. R., and Rugg, M. D. (2009). Selecting for memory? The influence of selective attention on the mnemonic binding of contextual information. *J. Neurosci.* 29, 8270–8279. doi: 10.1523/JNEUROSCI.1043-09.2009

von Allmen, D. Y., Wurmitzer, K., Martin, E., and Klaver, P. (2013). Neural activity in the hippocampus predicts individual visual short-term memory capacity. *Hippocampus* 23, 606–615. doi: 10.1002/hipo.22121

Vuilleumier, P., and Driver, J. (2007). Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 837–855. doi: 10.1098/rstb.2007.2092

Windmann, S., and Kutas, M. (2001). Electrophysiological correlates of emotion-induced recognition bias. *J. Cogn. Neurosci.* 13, 577–592. doi: 10.1162/089892901750363172

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Shared neural substrates of emotionally enhanced perceptual and mnemonic vividness

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It is well-known that emotionally salient events are remembered more vividly than mundane ones. Our recent research has demonstrated that such memory vividness (Mviv) is due in part to the subjective experience of emotional events as more perceptually vivid, an effect we call emotionally enhanced vividness (EEV). The present study built on previously reported research in which fMRI data were collected while participants rated relative levels of visual noise overlaid on emotionally salient and neutral images. Ratings of greater EEV were associated with greater activation in the amygdala and visual cortex. In the present study, we measured BOLD activation that predicted recognition Mviv for these same images 1 week later. Results showed that, after controlling for differences between scenes in low-level objective features, hippocampus activation uniquely predicted subsequent Mviv. In contrast, amygdala and visual cortex regions that were sensitive to EEV were also modulated by subsequent ratings of Mviv. These findings suggest shared neural substrates for the influence of emotional salience on perceptual and mnemonic vividness, with amygdala and visual cortex activation at encoding contributing to the experience of both perception and subsequent memory.

Keywords: memory, emotion, amygdala, visual cortex, emotional salience, affect-biased attention, emotionally enhanced memory, fMRI

INTRODUCTION

It is well-known that emotionally important events such as the birth of a child or September 11 hold a special place in memory (e.g., Brown and Kulik, 1977). There is substantial empirical evidence that emotionally salient stimuli or events are more likely to be remembered than mundane ones (Ochsner, 2000) and are remembered more vividly (Sharot et al., 2004, 2007; Kensinger et al., 2011).

There is also abundant evidence that emotional salience influences the initial perception of events. Emotions are associated with the mutually enhancing effects of sympathetic arousal (Anderson et al., 2006b) and increased attention (Pessoa et al., 2002; Anderson et al., 2003; Talmi et al., 2008), which results in facilitated encoding of emotional events (Anderson and Phelps, 2001; Anderson, 2005; De Martino et al., 2009; Lim et al., 2009). Emotionally important stimuli are also more easily detected and identified than neutral stimuli when attentional load is high (Soares and Ohman, 1993; Anderson, 2005), or stimuli are presented at the threshold of awareness (Nielsen and Sarason, 1981). At the neural level, human fMRI studies have shown that viewing emotionally salient images, such as scenes of mutilation or erotica, is associated with enhanced engagement of regions of visual cortex (Lang et al., 1998; Bradley et al., 2003; Vuilleumier et al., 2004; Sabatinelli et al., 2005; Padmala and Pessoa, 2008).

We have previously demonstrated that emotion-enhanced memory vividness (Mviv) in part reflects a subjective richness of perceptual experience, or emotionally enhanced vividness (EEV) (Todd et al., 2012). Using a magnitude estimation task in which low levels of visual noise were overlaid on neutral and emotionally salient scenes, we demonstrated that when objective levels of noise were equated, arousing images were experientially perceived as more perceptually vivid than neutral images (Todd et al., 2012). That is, participants subjectively perceived emotionally arousing images as containing greater signal (the underlying image) relative to overlaid noise. fMRI data revealed that, after controlling for low-level features of stimuli such as contrast, color, and scene complexity, EEV ratings were positively correlated with activity in left amygdala and lateral occipital cortex (LOC). Statistical mediation analyses suggested that amygdala activation accounted for the influence of visual cortex activation on EEV (Todd et al., 2012).

We also reported behavioral data indicating that EEV predicted subsequent Mviv, measured both by cued recall 45 min after encoding and recognition memory 1 week later (Todd et al., 2012). Previous studies have shown that enhanced memory for arousing images is associated with greater amygdala and visual cortex activation during encoding (Hamann et al., 1999; Canli et al., 2000; Kensinger et al., 2007b). Since our results showed that amygdala and visual cortex were modulated by EEV, an outstanding question concerned whether activity in these same regions predicts subsequent Mviv.

The present study built on a previously reported study (Todd et al., 2012), in which to measure EEV we adapted a magnitude

estimation paradigm designed to estimate human subjective estimates of graded magnitudes of sensory stimuli (Stevens, 1957). In each version of the noise estimation (NE) task, emotionally arousing (positive and negative) and neutral scenes were overlaid with sparse "visual noise," or randomly distributed pixels. Participants were asked to estimate the relative degree of "noisiness" of each picture in comparison to a standard image, which was created from scrambled versions of the scenes, matched in global luminance and contrast, overlaid with a varying levels of sparse noise (**Figure 1**). This provided a direct behavioral index of whether greater emotional salience results in greater perceptual vividness.

The goal of the present study was to investigate the link between the subjective experience of perceptual vividness and mnemonic vividness. Here we examined BOLD activation predicting Mviv ratings collected from an online recognition memory task 1 week after participants were scanned during the NE procedure in relation to activation evoked by EEV (for a timeline of the procedure, see **Figure 1B**). We predicted that amygdala and LOC activation would predict Mviv, along with additional brain regions, such as the hippocampus, also implicated in episodic memory (Lepage et al., 1998; Eldridge et al., 2005).

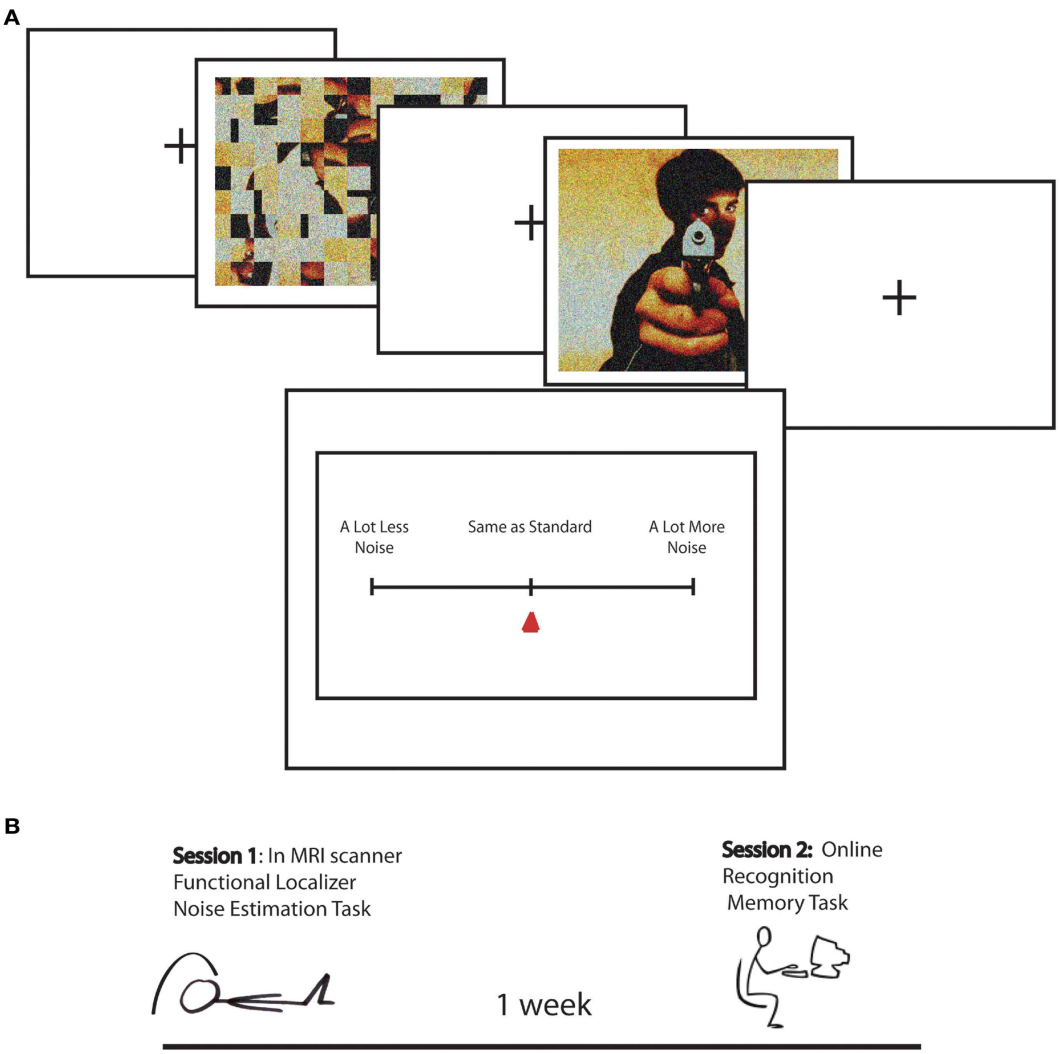


FIGURE 1 | (A) Task design for Noise Estimation fMRI experiment. A standard, created by phase scrambling the comparison image, was overlaid with 15% noise. The standard was followed by the image overlaid with 10, 15, or 20% noise. Following image offset, participants moved a cursor on a scale to indicated NE for the image relative to the standard from "a lot less noise" to "same as standard" to "a lot more noise." **(B)** Schematic of the study timeline over two sessions. In Session 1 participants performed the Noise Estimation task in the scanner. One week later they performed an online recognition memory task in which they were asked if images were old or new, and if they were old how vividly they were remembered on a scale from vague to detailed.

MATERIALS AND METHODS

fMRI STUDY

Participants

Eighteen healthy young adult volunteers from Queen's University (18–30 years) with normal or corrected to normal vision and no history of psychiatric disorders participated in this study. Two participants were removed from subsequent fMRI analysis: one had excessive movement and one misunderstood the task, leaving 16 participants (10 female).

Localizer task

In order to localize category-selective regions of visual cortex, we used a block design task that alternated blocks of line-drawings of objects and scrambled line-drawings to localize object-selective regions of the LOC. The task also included blocks of faces and houses to localize face and place selective regions of visual cortex respectively. Blocks alternated randomly to minimize category predictability and each image category was presented six times. Each 20 s block contained five images presented for 4000 ms each. In each block one of the images was repeated. To ensure that they were attending to the images presented onscreen, participants were asked to push a button with the index finger each time an image appeared if the image was not the same as the one immediately preceding it, and to press a second button with the middle finger if the image was identical to the one immediately preceding it. Because the behavioral task served merely as a vigilance task to maintain attention and maximize BOLD activation, behavioral results were not analyzed.

NOISE ESTIMATION TASK

Materials

Twenty-five negative photos and 25 positive photos were taken from the International Affective Picture System (IAPS). Twenty-five neutral photos were retrieved from the internet as well as the IAPS. A separate set of participants rated all pictures to be equal in brightness, contrast, and visual complexity, $Fs(2, 72) < 0.1$. Positive, negative, and neutral images were selected to be equivalent on basic low-level image statistics, equated in log luminance, $F(2, 72) < 1$, and RMS contrast, $F(2, 72) < 1$. One of three levels of Gaussian all-color noise (15%) was superimposed over each image using adobe Photoshop 7.0.

To minimize variance associated with differences in luminance and contrast across images, a standard was created to match each corresponding comparison image (**Figure 1**). Standards were created by phase scrambling each image and adding noise. Both standards and images subtended a visual angle of 13° × 9.5°. The level of noise on the pictures was held constant (15%) and noise level was varied in the standards (10, 15, 20%). Thus, we could measure BOLD responses related to estimations of perceptual and mnemonic vividness across images that did not vary in objective levels of noise.

Trials were presented in five separate runs of 30 trials. In order to reduce time spent into the scanner in this slow event-related design, each image was presented twice at two out of three levels of standard noise for a total of 150 trials (50 negative arousing, 50 positive arousing, and 50 neutral). Thus, each image was seen twice at 15% noise paired with a standard at two out of three possible noise levels (10, 15, and 20%). In each 12-s trial a standard was presented for 1500 ms, followed by a 500 ms ISI, followed by the picture which was presented for 1500 ms. Both standards and images subtended a visual angle of 13° × 9.5°. After a randomly jittered interval of 1500, 2000, or 2500 ms, a response meter appeared for 4000 ms, followed by a randomly jittered ITI of 2000, 2500, or 3000 ms. Participants clicked a button with the index finger to move the cursor to the left (less noisy than standard) and with the middle finger to move the cursor to the right (more noisy than standard), and a third button with the middle finger to indicate that the cursor was placed at the desired degree of noisiness. Fifty null trials (1/3), consisting of 12 s of fixation, were included at randomized intervals. After the scan participants were asked to log on to a website 1 week later.

Memory task

One week after performing the NE task, participants were instructed to log on to a website to complete a surprise memory task exactly 1 week after performing the NE task. An additional set of images, 12 positive, 12 neutral, and 12 negative, were matched with the Session 1 images for arousal, scene content, contrast, and luminance. Participants were shown the original 75 images and the 36 new images. After rating an image as new, familiar, or recollected, participants rated the vividness of the memory for recognized items on a scale of 1–7 (0 = new image), ranging from vague to detailed.

fMRI acquisition

Imaging data were collected with a 3T Siemens scanner using a 12-channel head coil. Both the localizer and experimental tasks were programed in E-prime Version 1.2 (Psychology Software Tools, Pittsburgh, PA, USA). For each subject, a three-dimensional magnetization prepared rapid-acquisition gradient-echo pulse sequence (MPRAGE) was used to acquire a high-resolution T1-weighted structural volume: repetition time (TR) = 1760 ms; echo time (TE) = 2.2 ms; FOV = 256 × 256; slice thickness = 1mm; 176 slices; total acquisition time = 7:32 min.

T2* weighted gradient-echo echo planar images were collected for two short field mapping series to correct for EPI distortion due to inhomogeneities in the magnetic field. Parameters for the field mapping series were: TR = 793 ms; TE1 = 5.19 ms, and TE2 = 7.65 ms; flip angle = 60; FOV = 211 mm. Thirty-five slices were acquired with a voxel size of 3.3 mm × 3.3 mm × 3.5 mm. EPI parameters for the two functional tasks were: TR = 2000 ms; TE = 25 ms; flip angle = 78°; FOV = 211mm. Thirty-five slices were acquired with a voxel size of 3.3 mm × 3.3 mm × 3.5 mm.

Preprocessing

Data were analyzed with Statistical Parametric Mapping software (SPM8, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/sofware/spm8). Slice timing correction of reconstructed images was performed after removing the first five time points from each functional run. Field maps were unwarped with the EPI time series and time series were realigned for motion and field distortion correction. T1-weighted structural images were co-registered to the EPI images, and then bias

corrected and segmented using MNI template tissue probability maps. EPI images were then co-registered to the normalized segmented anatomical images. Finally, time series data were smoothed with a 6 mm full-width half maximum Gaussian kernel.

First-level statistical models

For each subject, first-level general linear models were applied to localizer data and data from the NE task. For the localizer data, boxcar stimulus functions were convolved with the canonical hemodynamic response function (HDR). Our goal was to compare regions correlated trial by trial with Mviv ratings with previously patterns of parametric modulation by emotionally enhanced perceptual vividness. We thus examined parametric modulation of the BOLD response by both perceptual and mnemonic vividness ratings for each trial across all stimulus categories (positive, negative, and neutral). For the experimental data, a delta function regressor was modeled for image onset and convolved with the canonical HRF for each trial in each analysis. For each subject, we created a first-level statistical parametric model (SPM). To capture variance due to low-level features of the images which could influence our results, we first entered four separate regressors modeling scene complexity, hue, contrast, and mean visual saliency (a measure of a combination of features that allow a part of an image to stand out from its surround) (Itti and Koch, 2001). We next entered a regressor for Mviv to interrogate regions parametrically modulated by mnemonic vividness. An additional regressor was added for perceptual vividness, or inverse NE (NE^{-1}) (for details, see Todd et al., 2012) to further interrogate effects of Mviv relative to NE^{-1}. Full results of group level analysis reported below can be found in **Tables 1** and **2**.

Second-level statistical models

For the localizer task, *T* contrast files for each condition (object drawings, scrambled objects, places, and faces) from each individual were entered into a one-way ANOVA, with condition as the single factor. Contrasts for (objects > scrambled objects) were used to specify category-selective activation in the LOC. An additional contrast was used to specify place-sensitive regions of parahippocampal cortex (houses > faces). Functionally defined masks were created using 10 mm spheres around maxima activations in the group maps (51, −76, 1 and −45, −79, 1) thresholded at $p < 0.05$ (FWE). Anatomical masks for right and left amygdala and right and left hippocampus were created from automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) templates based on a spatially normalized high-resolution T1 single-subject data set using the MarsBaR toolbox (Brett et al., 2002). Together, these ROIs were used for small volume correction for the NE task.

To orthogonalize their comparison, contrast files for Mviv and NE^{-1} from a single first-level model were used. To enable contrasts between activation enhanced by each parametric modulator, contrast files were entered into a one-way repeated measures ANOVA (independence not assumed) at the group level. Initial SPMs were thresholded at a height threshold of $p < 0.005$, uncorrected, with a cluster extent threshold of 10 voxels (for rationale, see Lieberman and Cunningham, 2009). Primary results for hypothesized regions were corrected for family-wise error. Functionally and anatomically defined ROIs were used as masks for small volume correction based on *a priori* hypotheses. Voxels surviving a family-wise error corrected $p < 0.05$ were deemed statistically significant.

Table 1 | Regions parametrically modulated by Mviv > Pviv.

Brain region	*x*	*y*	*z*	Voxels	*t*	*p*
L lingual-parahippocampal gyrus-hippocampus/BA 37	−27	−52	−5	70	5.01	<0.001
R inf orbital gyrus/BA 47	30	29	−20	16	3.87	<0.001
L middle occipital gyrus/BA 18–19	−30	−91	19	43	3.79	<0.001
R fusiform-parahippocampal gyrus/BA 37	30	−40	11	23	3.46	0.001

Table 2 | Regions parametrically modulated by Pviv > Mviv.

Brain region	*x*	*y*	*z*	Voxels	*t*	*p*
L insula/BA 48	−36	−19	22	37	4.74	<0.001
L sup temporal gyrus/BA 48	−51	−13	−2	143	4.47	<0.001
R sup temporal gyrus-Heschl gyrus/BA 48	51	−22	1	35	3.29	0.001
R sup temporal pole/BA 38	54	8	−11	13	2.87	0.002

xyz = MNI coordinates. Cluster size as thresholded at p < 0.005, uncorrected.

RESULTS

BEHAVIORAL RESULTS

Noise estimation task

A two factor repeated measures ANOVA was performed on NE with standard noise (3) and emotion (3) as factors. Results showed a main effect of standard noise, $F(2, 28) = 28.42$, $p < 0.001$. A significant linear contrast, $F(1, 14) = 32.01$, $p < 0.001$, revealed noise ratings of the images to be relatively lower relative to the standard as standard noise levels got higher, again indicating that participants were accurate at gaging relative noise even when noise level was manipulated in the standard. There was also a main effect of emotion, $F(2, 28) = 10.32$, $p < 0.001$, with arousing images rated as less noisy – or more perceptually vivid – than neutral images, $F(1, 14) = 12.50$, $p = 0.003$. A modest standard noise × emotion interaction, $F(4, 56) = 4.26$, $p < 0.05$, revealed differences between positive and neutral images to be greater at the two lower levels of standard noise. Contrasts revealed that, as in previous studies both positive and negative images were rated as less noisy, or more vivid, than neutral images, ps < 0.05; unlike in previous studies, negative images were also rated as more vivid than positive images, $p < 0.05$.

Memory

A one-way ANOVA was performed on Mviv scores with emotion as a repeated measure. There was a main effect of emotion category, $F(2, 28) = 9.33$, $p = 0.001$. Contrasts revealed that negative images were remembered more vividly than neutral or positive images, $F(1, 14) = 20.82$, $p = 0.001$. There was no effect of emotion category on memory accuracy.

fMRI RESULTS

Perceptual and mnemonic vividness

As previously reported, higher levels of NE^{-1} were associated with more activation in the left amygdala ($xyz = -24, -4, -20$) and left LOC ($xyz = -51, -76, -2$). Regions where greater activation was associated with higher levels of Mviv similarly included the left amygdala ($-21, -4, -17$; $t_{1,28} = 3.21$, FWE $p = 0.02$, svc) and left LOC ($-39, -79, -5$; $t_{1,28} = 3.23$, FWE $p = 0.04$, svc). To more closely examine the relation between regions modulated by memory and perceptual vividness, the contrast for Mviv was masked inclusively by activation for NE^{-1}at a threshold of $p = 0.005$, uncorrected. All voxels activated by memory in the left amygdala and LOC fell within regions that were activated by perceptual vividness. As **Figures 2D,E** demonstrates, Mviv shows a highly similar pattern of activation to NE^{-1} in the left amygdala and left LOC. These voxels were also activated significantly in both conditions when analyzed separately.

To reveal regions uniquely recruited by Mviv, comparisons between Mviv and NE^{-1} revealed that a region of left hippocampus ($-30, -37, -8$; $t_{1,28} = 3.36$, FWE $p = 0.05$, svc) and a place-sensitive region of left parahippocampal gyrus ($-27, -52, -5$; $t_{1,14} = 5.33$, FWE $p = 0.05$, svc) were activated more for Mviv than

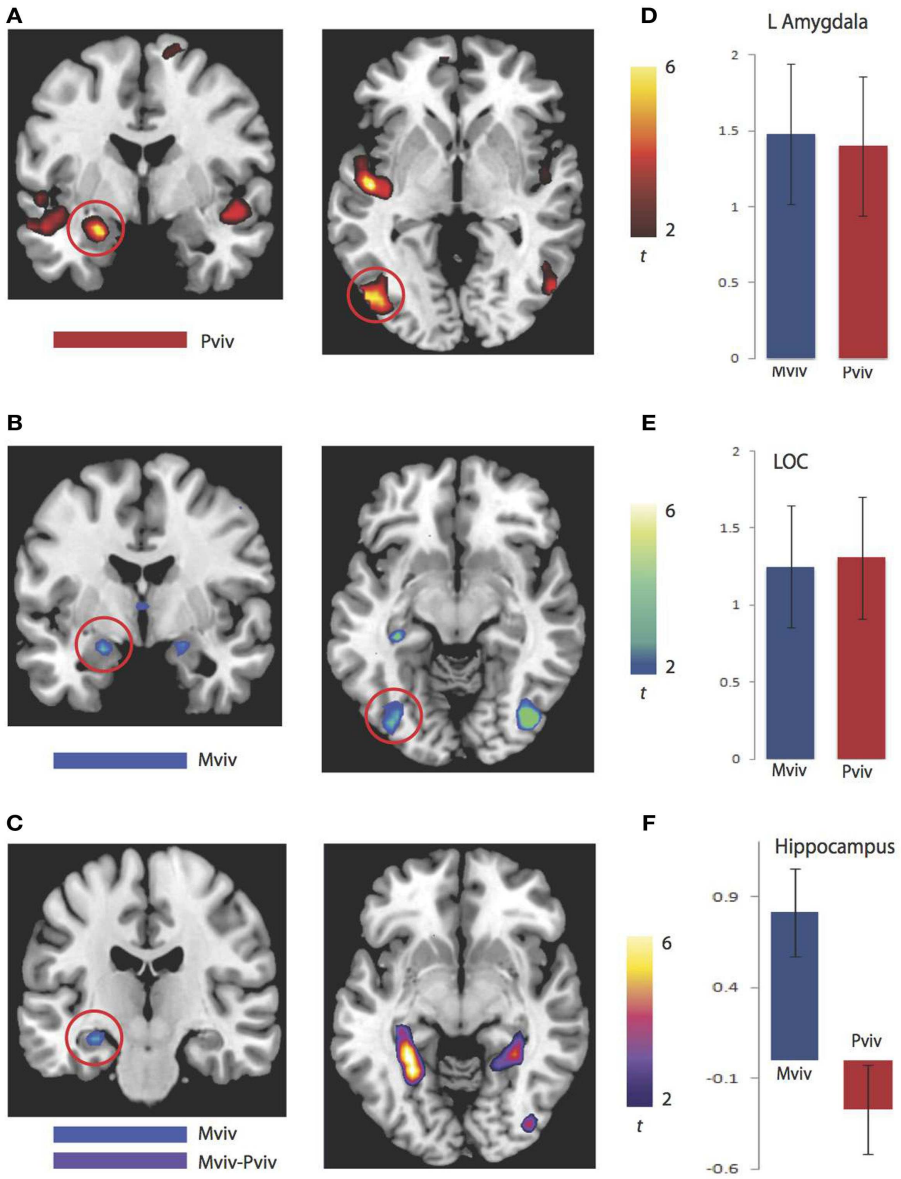


FIGURE 2 | BOLD correlates of perceptual and memory vividness. **(A)** Activation maps for regions parametrically modulated by perceptual vividness. **(B)** Activation maps for regions parametrically modulated by memory vividness. **(C)** Activation maps showing hippocampal region activated by Mviv and regions activated by the contrast Mviv > Pviv. **(D)** Contrast estimates for Pviv and Mviv for left amygdala. **(E)** Contrast estimates for Pviv and Mviv for left LOC. **(F)** Contrast estimates for Mviv and Pviv for left hippocampal region activated by Mviv.

NE^{-1} (**Figure 2**). Thus, consistent with our previously reported behavioral evidence of partial independence between EEV and Mviv, only a subset of regions activated by Mviv also reflected EEV.

DISCUSSION

Our results showed that, after controlling for differences between scenes in low-level objective features, amygdala and visual cortex regions that were sensitive to EEV were also modulated by ratings of subsequent Mviv. In contrast, hippocampus activation uniquely predicted Mviv. These findings suggest shared neural substrates for the influence of emotional salience on perceptual and mnemonic vividness, with amygdala and visual cortex regions associated with EEV at encoding contributing to the experience of emotionally enhanced memory.

Emotionally salient images (both positive and negative) are more likely to be remembered than neutral images (Ochsner, 2000). In particular, emotionally salient images have been linked to greater memory for the central, emotionally salient, or goal-relevant elements of a scene (Kensinger et al., 2007a; Levine and Edelstein, 2009). Such findings have been associated with greater amygdala activation (Hamann et al., 1999; Canli et al., 2000; Kensinger et al., 2007b) as well as high-order visual cortex activation at encoding (Kensinger et al., 2007b; Talmi et al., 2008), and suggest that perceptual processing of emotionally important events may be related to heightened memory (Kensinger et al., 2007b). Here we provide novel evidence for a direct mapping between emotion-enhanced perceptual vividness and mnemonic vividness.

Yet this finding is in contrast to a levels of processing framework (Craik and Lockhart, 1972), where it is categorization at a deeper conceptual level rather than shallower perceptual level that yields enhanced memory. Rather, our data suggest that emotional salience is associated with a unique behavioral and neural expression of memory. High levels of emotional salience, as tagged by the amygdala, may heighten the binding between objects, their meaning, and emotional significance (Nashiro and Mather, 2011), yielding a unique subjective vividness to both perception and memory.

In previous studies we found no differences between noise estimation ratings for positive and negative images (Todd et al., 2012). In the present study, although both positive and negative images were rated as less noisy than neutral images, negative images were further rated as less noisy, or more perceptually vivid, than positive images. This pattern of stronger results for negative stimuli extended to the memory findings in which negative images were more vividly remembered 1 week later than positive or negative images. Because of our parametric analysis across all trial types, we cannot report the extent to which image valence may have contributed to the pattern of results found here. Previous studies looking at emotionally enhanced memory have found amygdala activation at encoding to be associated with subsequent memory for both negative and positive stimuli (Hamann, 2001).

As previously reported, amygdala activation accounted statistically for the relation between LOC activation and EEV at the time of encoding (Todd et al., 2012). Although it is not possible to infer directionality from a mediation analysis, one hypothesis is that the enhanced visual cortex activation associated with EEV is amygdala-driven, and that a similar modulation of visual cortex by the amygdala produces subsequent Mviv. This hypothesis is consistent with a body of non-human animal research finding that emotional memory is characterized by arousal-enhanced noradrenergic activity in the basolateral amygdala, which in turn modulates activation in other brain regions implicated in memory consolidation, including the hippocampus and sensory cortices (Cahill and McGaugh, 1998; McGaugh et al., 2002; Roozendaal and McGaugh, 2011). Yet other human studies looking at emotionally enhanced perceptual activations under attentionally impoverished conditions have found a slightly different pattern of findings, with prefrontal mediation of the relation between the amygdala and visual cortex (Lim et al., 2009). Future research can use such approaches as dynamic causal modeling to investigate the directionality of amygdala influences on perceptual and mnemonic vividness.

It is important to highlight that our previously reported behavioral findings suggested that enhanced perceptual vividness contributes to, but does not entirely account for, the heightened salience of emotional memories (Todd et al., 2012). This is consistent with the current finding that the hippocampal and parahippocampal regions specifically implicated in memory formation and its emotional enhancement (Kensinger et al., 2007b; Talmi et al., 2007; Murty et al., 2010) were modulated by mnemonic – but not perceptual – vividness. Research in non-human animals (McGaugh et al., 2002) and humans (Cahill and Alkire, 2003; Anderson et al., 2006a) also indicates that arousal induced *after* encoding influences memory consolidation to alter memory retention, which by definition cannot be explained by vivid perceptual encoding. Phasic arousal related to perceptual vividness may interact with more tonic arousal extending beyond initial encoding to alter memory consolidation (Cahill and Alkire, 2003), mutually enhancing later memory. Thus, the influence of affective salience at encoding likely occurs at multiple timescales, which combine to endow emotional experiences and their associated memories with a uniquely vivid subjective character. Future research can delineate how individual differences in effects of arousal on perceptual vividness and post-encoding processes may be linked to normative differences in capacity for emotional memory as well as the prevalence of intrusively vivid memories following trauma (Nashiro and Mather, 2011; Todd et al., 2011).

REFERENCES

Anderson, A. K. (2005). Affective influences on the attentional dynamics supporting awareness. *J. Exp. Psychol. Gen.* 134, 258–281.

Anderson, A. K., Christoff, K., Panitz, D., De Rosa, E., and Gabrieli, J. D. (2003). Neural correlates of the automatic processing of threat facial signals. *J. Neurosci.* 23, 5627–5633.

Anderson, A. K., and Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 411, 305–309.

Anderson, A. K., Wais, P. E., and Gabrieli, J. D. (2006a). Emotion enhances remembrance of neutral events past. *Proc. Natl. Acad. Sci. U.S.A.* 103, 1599–1604.

Anderson, A. K., Yamaguchi, Y., Grabski, W., and Lacka, D. (2006b). Emotional memories are not all created equal: evidence for selective memory enhancement. *Learn. Mem.* 13, 711–718.

Bradley, M. M., Sabatinelli, D., Lang, P. J., Fitzsimmons, J. R., King, W., and Desai, P. (2003). Activation of the visual cortex in motivated attention. *Behav. Neurosci.* 117, 369–380.

Brett, M., Anton, J.-L., Valabregue, R., and Poiine, J.-B. (2002). Region of interest analysis using an SPM toolbox [abstract]. *Paper presented at the 8th International Conference on Functional Mapping of the Human Brain*, Sendai.

Brown, R., and Kulik, S. (1977). Flashbulb memory. *Cognition* 5, 73–99.

Cahill, L., and Alkire, M. T. (2003). Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiol. Learn. Mem.* 79, 194–198.

Cahill, L., and McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* 21, 294–299.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., and Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *J. Neurosci.* 20, RC99.

Craik, F. I., and Lockhart, R. S. (1972). Levels of processing: a framework for memory research. *J. Verbal Learning Verbal Behav.* 11, 671–684.

De Martino, B., Kalisch, R., Rees, G., and Dolan, R. J. (2009). Enhanced processing of threat stimuli under limited attentional resources. *Cereb. Cortex* 19, 127–133.

Eldridge, L. L., Engel, S. A., Zeineh, M. M., Bookheimer, S. Y., and Knowlton, B. J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *J. Neurosci.* 25, 3280–3286.

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends Cogn. Sci. (Regul. Ed.)* 5, 394–400.

Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* 2, 289–293.

Itti, L., and Koch, C. (2001). Computational modelling of visual attention. *Nat. Rev. Neurosci.* 2, 194–203.

Kensinger, E. A., Addis, D. R., and Atapattu, R. K. (2011). Amygdala activity at encoding corresponds with memory vividness and with memory for select episodic details. *Neuropsychologia* 49, 663–673.

Kensinger, E. A., Garoff-Eaton, R. J., and Schacter, D. L. (2007a). Effects of emotion on memory specificity: memory trade-offs elicited by negative visually arousing stimuli. *J. Mem. Lang.* 56, 575–591.

Kensinger, E. A., Garoff-Eaton, R. J., and Schacter, D. L. (2007b). How negative emotion enhances the visual specificity of a memory. *J. Cogn. Neurosci.* 19, 1872–1887.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., et al. (1998). Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology* 35, 199–210.

Lepage, M., Habib, R., and Tulving, E. (1998). Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 8, 313–322. [Meta-Analysis Research Support, Non-U.S. Gov't].

Levine, L. J., and Edelstein, R. S. (2009). Emotion and memory narrowing: a review and goal relevance approach. *Cogn. Emot.* 23, 833–875.

Lieberman, M. D., and Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc. Cogn. Affect. Neurosci.* 4, 423–428.

Lim, S. L., Padmala, S., and Pessoa, L. (2009). Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. *Proc. Natl. Acad. Sci. U.S.A.* 106, 16841–16846.

McGaugh, J. L., McIntyre, C. K., and Power, A. E. (2002). Amygdala modulation of memory consolidation: interaction with other brain systems. *Neurobiol. Learn. Mem.* 78, 539–552.

Murty, V. P., Ritchey, M., Adcock, R. A., and LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: a quantitative meta-analysis. *Neuropsychologia* 48, 3459–3469.

Nashiro, K., and Mather, M. (2011). How arousal affects younger and older adults' memory binding. *Exp. Aging Res.* 37, 108–128.

Nielsen, S. L., and Sarason, I. G. (1981). Emotion, personality, and selective attention. *J. Pers. Soc. Psychol.* 41, 945–960.

Ochsner, K. N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J. Exp. Psychol. Gen.* 129, 242–261.

Padmala, S., and Pessoa, L. (2008). Affective learning enhances visual detection and responses in primary visual cortex. *J. Neurosci.* 28, 6202–6210.

Pessoa, L., Kastner, S., and Ungerleider, L. G. (2002). Attentional control of the processing of neural and emotional stimuli. *Brain Res. Cogn. Brain Res.* 15, 31–45.

Roozendaal, B., and McGaugh, J. L. (2011). Memory modulation. *Behav. Neurosci.* 125, 797–824.

Sabatinelli, D., Bradley, M. M., Fitzsimmons, J. R., and Lang, P. J. (2005). Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance. *Neuroimage* 24, 1265–1270.

Sharot, T., Delgado, M. R., and Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nat. Neurosci.* 7, 1376–1380.

Sharot, T., Martorella, E. A., Delgado, M. R., and Phelps, E. A. (2007). How personal experience modulates the neural circuitry of memories of September 11. *Proc. Natl. Acad. Sci. U.S.A.* 104, 389–394.

Soares, J. J., and Ohman, A. (1993). Backward masking and skin conductance responses after conditioning to nonfeared but fear-relevant stimuli in fearful subjects. *Psychophysiology* 30, 460–466.

Stevens, S. S. (1957). On the psychophysical law. *Psychol. Rev.* 64, 153–181.

Talmi, D., Anderson, A. K., Riggs, L., Caplan, J. B., and Moscovitch, M. (2008). Immediate memory consequences of the effect of emotion on attention to pictures. *Learn. Mem.* 15, 172–182.

Talmi, D., Schimmack, U., Paterson, T., and Moscovitch, M. (2007). The role of attention and relatedness in emotionally enhanced memory. *Emotion* 7, 89–102.

Todd, R. M., Palombo, D. J., Levine, B., and Anderson, A. K. (2011). Genetic differences in emotionally enhanced memory. *Neuropsychologia* 49, 734–744.

Todd, R. M., Talmi, D., Schmitz, T. W., Susskind, J., and Anderson, A. K. (2012). Psychophysical and neural evidence for emotion-enhanced perceptual vividness. *J. Neurosci.* 32, 11201–11212.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* 7, 1271–1278.

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Development in the organization of episodic memories in middle childhood and adolescence

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The basic elements of autobiographical or episodic memory are established in early childhood, although the exact age at which memories gain episodic status is still under contention. The self-memory system proposed that adults use "lifetime periods" to group episodic memories together into chapters of the life story – an evolving and internalized account of significant life events that are self-defining. Two studies examined at what point in development children or adolescents begin to take advantage of lifetime-period chapters to organize their episodic memories. The results of Study 1 with 8- to 12-year-olds revealed that the ability to provide life story chapters began to emerge as early as 8 years of age. In Study 2 with adolescents aged 12–21, this ability continued to develop into late adolescence among New Zealand European (NZE) and New Zealand Chinese (NZC) adolescents; however, cultural differences also existed in the specificity of memories. NZC adolescents narrated fewer life story chapters containing specific memories than NZE adolescents. These findings support and extend current theories of episodic memory by specifying that pre-adolescents are starting to organize their episodic memories into lifetime periods, but this achievement is not fully realized until later in adolescence.

Keywords: episodic memory, self-memory system, culture, middle childhood, adolescence, life story

INTRODUCTION

Episodic memory requires the ability to mentally travel back in time to locate a past event and to be able to provide information about the *what*, *when*, and *where* aspects of that event (Tulving, 1985, 2002). An important feature that separates episodic memory from other types of memory is the experience of subjective remembering, also referred to as autonoetic consciousness. In other words, episodic memory depends on individual awareness of a continuous self over time and the ability to mentally re-experience the recalled event (Wheeler et al., 1997). Episodic memories that are self-relevant are referred to as autobiographical memories (Nelson and Fivush, 2004). The age at which true episodic/autobiographical memory emerges in development is still under debate. Some theorists claim that episodic memory emerges between the age of 4 and 6, when autonoetic consciousness is developed (Perner and Ruffman, 1995; Perner, 2001; Tulving, 2005). Tulving further proposed that episodic memory entailing autonoetic awareness is preceded by development of a generalized knowledge base (semantic memory). Other theorists assert that episodic memory is possible earlier in development, by age 3 (Scarf et al., 2013), age 2 (Howe and Courage, 1993, 1997), or even before birth (Conway, 2009). Nonetheless, all theorists agree that by the time children are of school age, they are clearly capable of episodic remembering (Piolino et al., 2007). The main aim of the present paper is to trace the continued developments in episodic remembering in middle childhood and adolescence, after episodic remembering accompanied by autonoetic awareness is possible, and specifically to explore the development of the organization of episodic memories.

Conway and colleagues proposed the *Self-Memory System* theory to describe the organization of autobiographical memory, which suggests that different memory structures co-exist in a hierarchy in the long-term memory system (see Conway and Pleydell-Pearce, 2000; Conway, 2005, 2009; for reviews). The self-memory system theory specifies that single episodic memories (i.e., memories of specific events, such as the first day of school) are placed at the lowest level, followed by general, recurring events (e.g., going to school) that are nested within different lifetime periods (e.g., primary school days), which together contribute to various themes that are part of the life story. The life story is an evolving account of the events in one's life that are currently self-defining. Note that Conway and colleagues assert that specific memories are more fundamental in the self-memory system than are general events, in the sense that general events are made up of specific instances. For example, celebrating my 21st birthday is an episodic memory that contributes to the general event of "going to parties," which is part of a lifetime period such as "my university years." Ultimately, different lifetime periods (e.g., my university years, my teenage years, and my childhood) form the outline of a person's life story. Episodic memories, general events, lifetime periods, and the life story are all part of the *autobiographical knowledge base* (Conway, 2009). The autobiographical knowledge base contains self-relevant facts (e.g., birthdate, name of school, and family members), as well as episodic memories relating to the self. In the current paper, we investigated the development of the organization of episodic memories, as defined by Tulving (1985), within the framework of the self-memory system theory. Below, we review the self-memory

system theory and evidence to support this theory based on adult samples.

The different components of the self-memory system theory have been examined in terms of the structure of adults' life stories in Thomsen (2009). In this study, 30 elderly Danish adults were asked to tell their life stories, without specific instructions on the structure or content of the life story. Chapters were the most common way of structuring the life story; they were thematically organized to cover particular periods of one's life. Specific memories also featured in the chapters. However, the number of specific memories was not related to the number of chapters, suggesting that chapters and specific memories were equally important for the construction of the life story. Thomsen suggested that specific memories are the building blocks of the life story, and that chapters are organized based on a common theme extracted from various specific memories. Thomsen further argues that chapters are the preferred structure for organizing an outline for the life story, because chapters require less memory storage than specific memories. Moreover, Thomsen et al. (2011) found that specific memories tended to cluster at the beginning of chapters, indicating that chapters based on lifetime periods trigger the recall of specific autobiographical memories.

Specific autobiographical memories, which are also referred to as episodic memories, emerge in the preschool years and continue to develop in important ways during middle childhood. For instance, Piolino et al. (2007) noted that in middle childhood memories become more detailed in their inclusion of episodic elements. Other research has found that older children and adolescents require less prompting to retrieve specific memories (Willoughby et al., 2012). Middle childhood and early adolescence is also a critical time to develop the ability to organize discrete episodic memories in chronological and meaningful ways in order to construct the life story (Habermas and Bluck, 2000). For example, by age 12, autobiographical narratives within the life story become integrated with respect to time and place (i.e., chronology); however, thematic and causal integration (i.e., meaning of past events for self) develop later in adolescence (Habermas and de Silveira, 2008). Although there is evidence supporting the hierarchical structure of long-term memory in adulthood, little is known about the developmental trajectory of this process. The first goal of the current research, therefore, is to track the development of episodic memories in relation to the autobiographical knowledge base by examining when school-age children and adolescents begin to use lifetime periods to organize their episodic memories, which ultimately form the basis of their life stories.

Apart from cognitive maturation that contributes to the hierarchical structure of long-term memory, culture also influences this developmental process as autobiographical memories are constructed within a sociocultural context (Fivush and Nelson, 2004). Cultural variations in autobiographical memory are found in terms of the socialization processes that foster the development of autobiographical memory, such as parent-child joint reminiscing (Mullen and Yi, 1995; Fivush and Wang, 2005; Kulkofsky et al., 2009). Cultural differences are also present in the content and structure of the autobiographical memory. People from Western cultures, for example, recall earlier first memories, and those memories are more elaborative and emotion laden, compared to their Eastern counterparts (Mullen, 1994; MacDonald et al., 2000; Wang, 2006b). Also, people from Western cultures recall autobiographical memories that are based on specific events and are self orientated, whereas people from Eastern cultures are more likely to recall autobiographical memories that are based on generic events and are socially orientated (Wang, 2006a). Cultural differences in perceiving the self relative to others are believed to be the underlying factor causing cultural variations in the recollection of autobiographical memory (Markus and Kitayama, 1991; Wang, 2008).

Cultural differences in memory recollection are also found at the encoding phase. For example, Wang (2009a) conducted a diary study in which European American and Asian college students were asked to list specific, one-time events that happened during the day for seven consecutive days. The results showed that Asian students recorded fewer specific memories in their diaries compared to the European American students, whereas both groups showed a similar forgetting rate when they were asked to recall these events 1 and 2 weeks later. This evidence suggests that cultural variation in memory density is possibly due to cultural differences in encoding rather than the ability to retain memories in the long-term memory system. Furthermore, when asked to recall a fictional story, Asian students recalled the story with fewer segments than did the European American students. This is consistent with Nisbett and Miyamoto's (2005) claim that Asians are more likely to adopt a holistic processing style (i.e., details of the story are integrated and processed as a whole such that only the gist of the story is remembered), whereas European Americans are more likely to adopt an analytical processing style (i.e., salient features of the story are remembered separately). Given these cultural differences in the content of episodic memory, a second goal of this research was to investigate cultural differences in the structure of long-term memory among in adolescents from two cultures: New Zealand European (NZE) and New Zealand Chinese (NZC).

In Study 1, using the Emerging Life Story Interview protocol (ELSI; Reese et al., 2010), we asked 8- to 12-year-old children to tell us their life stories as if they were chapters from a book. Life story structure was assessed on two dimensions: (1) for the use of lifetime-period (LP) chapters (e.g., my high school years) as opposed to single-event (SE) chapters (e.g., a family trip to Australia); and (2) for the presence of specific memories. Note that these two dimensions are not mutually exclusive. All of the LP chapters contained general memories; some of the LP chapters contained general as well as specific memories; SE chapters contained one or more specific memories. We created the following two variables to capture the structure of the life story: (1) chapters based on lifetime periods versus chapters based on single events, and (2) chapters containing specific memories. We hypothesized that there would be age-related increases in children's use of LP chapters versus SE chapters as the main structure of the life story, and potentially also in the inclusion of specific memories within chapters as episodic memory continued to develop across this age period.

In Study 2, life stories were elicited from NZE and NZC adolescents, aged between 12 and 21. Again, we hypothesized age-related increases in using LP chapters for both cultural groups. We predicted that NZE adolescents would have more chapters in the life

story compared to NZC adolescents, due to the cultural differences in cognitive processes (Wang, 2009a). Based on previous research on the specificity of memory (Wang, 2006a), we also predicted more chapters containing specific memories to be present in the life stories of NZE participants.

STUDY 1

METHOD

Ethics statement

Study 1 and Study 2 were approved by the University of Otago Human Ethics Committee.

Participants

One hundred and twenty four children (69 girls and 56 boys), aged between 8 and 12 years old, and their mothers participated in the present study. Children were recruited from several local primary and intermediate public schools in Dunedin, New Zealand. The average age across the whole sample was 10.55 years, with a mean age of 10.60 years for girls (SD = 1.46) and 10.50 years for boys (SD = 1.40). The majority of the children were of NZE descent ($N = 106$); other ethnicities included Māori ($N = 2$), British ($N = 2$), Asian ($N = 1$), and mixed ($N = 12$). Most mothers had completed high school education or beyond ($N = 118$). Family socio-economic status was measured by the Elley-Irving Socio-Economic 2001 Index (Elley and Irving, 2003); the average score was 2.5 on a six-point scale, ranging from one (highly skilled professional; e.g., lawyer) to six (unskilled labor; e.g., shearing shed worker). Written parental and child consents were obtained before the interview. Each family received a small gift at the end of the interview session.

Procedure

Children and their mothers visited our lab for a single interview session, where they were greeted by two female interviewers. This research was part of a larger study (see Friedman et al., 2011 for details) and only measures pertinent to children's life stories are mentioned here. After signing the consent forms, the parent went to a separate room with one interviewer, while the child stayed in the main laboratory with another interviewer. The child and parent interviews were conducted simultaneously. Children were interviewed about their life stories and specific life-changing events.

Measures

Life story chapters. Children's life stories in this research were elicited using the Emerging Life Story Interview (ELSI, Reese et al., 2010, adapted from McAdams, 1996). In the ELSI, children were instructed to tell a story of their life as if it were a story in a book. Specifically, children were asked to divide the life story into different chapters. The interview always started with the chapter that the child was currently in. Then she or he could choose how to narrate the rest of the chapters by working backwards to the chapter that came before the current one, until reaching the first chapter. Once the child had nominated a chapter, she or he was asked to describe the important events that had happened in that chapter. They were also asked to offer a title for the chapter. There was no minimum requirement on the number of chapters, but the maximum number of chapters was kept at 10. The interviewer wrote down the structure of the life story while the interview was audiotaped, including the name and the content of each chapter on a summary sheet. Once the child had finished narrating the chapters, the interviewer recapped the entire life story starting from the earliest chapter, so that the child had a chance to correct or add new information to the life story.

Language ability. Form B of the Peabody Picture Vocabulary Test (PPVT), Fourth Edition (Dunn and Dunn, 2007) was used to assess participants' language skills because language is an important medium for the development of memory, and vocabulary is related to young children's recall of past events (Reese, 2002; Nelson and Fivush, 2004). The PPVT is an oral assessment of receptive language that is highly correlated with language ability and verbal IQ (Smith et al., 1991). Children were shown a set of four pictures and asked to indicate which picture best described the word that the experimenter had just told them. There was no time limit for the PPVT, and the test terminated when there were over eight or more errors in a set of 12 words. Standard scores were used in analyses.

Coding

The life stories were not transcribed, as we were interested in the organization rather than the content of children's autobiographical memory. Coding was conducted based on information the interviewer wrote down on the summary sheet during the interviews about the title, chapters, and memories within each chapter. Gender and other identifying information (such as the name of the child or siblings) were removed from the forms for coding.

Each chapter was coded as either *Lifetime Period* or *Single Event*. LP chapters contained several events that occurred over a certain time frame, ranging from a few months to a few years (e.g., my primary school years). These events also needed to be connected with each other in some way in order to form an overarching theme. As mentioned earlier, LP chapters contain general memories or a mixture of general and specific memories. In contrast, SE chapters contained discrete events that did not converge to an overall theme. Quite often, there was only one event listed for each chapter, typically lasting for less than a day (e.g., a trip to Movie World). Note that general event memory (i.e., semantic memory) is suggested as the developmental precursor of episodic memory (Tulving, 2005; although see Conway, 2009 for an alternative view). This claim is derived from research on cued recall and on the content of the recollection. In contrast, our investigation focused on the organization of memory, which is hierarchically constructed from episodic memories as suggested by the self-memory system theory. In line with Conway's approach, we consider LP chapters to be more developmentally advanced than SE chapters, despite the fact that LP chapters contain general event memories.

We then coded chapter specificity to capture whether each chapter contained one or more specific memories. In Conway's (2009) theory, specific episodic memories are the building blocks of general event knowledge, which ultimately develops into an abstract form of self-knowledge, namely an individual's life story. General events are also the preferred structure for long-term memory as they require less cognitive load for memory storage

(Conway et al., 2004). As a result, age-related changes were expected for the structure of life stories, such that younger children would initially organize their chapters based on specific events and older children would be more likely to use general event knowledge to represent life story chapters. Note that we did not require evidence of participants' autonoetic consciousness as a selection criterion for specific memory. Rather, all memories describing specific, one-point-in-time events were considered as specific episodic memories. This is due to the fact that true episodic/autobiographical recollection should be well developed in the age range of our participants (Perner, 2001; Piolino et al., 2007).

Two coders coded 25% of the life story chapters to reach reliability in terms of the numbers of LP chapters versus SE chapters and the number of chapters containing specific memories. Percentage agreement was calculated at above 90% for both categories. Disagreements were resolved through discussions between the coders. Once reliable, the two coders each coded 50% of the remaining life story chapters.

RESULTS

Preliminary analyses

Univariate analysis of variance (ANOVA) showed a marginal main effect of age on the proportion of LP chapters [$F(4, 119) = 2.10$, $p = 0.09$]. Fisher's LSD tests showed that children in the 8-, 9-, and 10-year-old groups reported significantly smaller proportions of life-period chapters than those in the 12-year-old group, whereas there were no significant differences between children in the 11-year old group and either the older or younger age groups. See **Figure 1** for the proportions of LP chapters reported by children from each age. Based on this finding, we decided to dichotomize the sample into two age groups, with the middle childhood group consisting of 8-, 9-, and 10-year-old children ($M = 9.62$, SD $= 0.84$, $N = 76$) and the early adolescence group consisting of 11- and 12-year-old children ($M = 12.11$, SD $= 0.59$, $N = 48$), for all further analyses.

Children's receptive language skills, as measured by the PPVT, did not differ significantly as a function of age group or gender. However, there was a significant interaction between age group and gender [$F(1, 117) = 5.15$, $p < 0.05$, partial $\eta^2 = 0.04$]. Children's PPVT scores did not differ between boys ($M = 108.03$, SD $= 11.69$) and girls ($M = 111.60$, SD $= 11.72$) in the middle childhood group. In contrast, boys scored slightly higher ($M = 114.85$, SD $= 12.81$) than did girls ($M = 107.85$, SD $= 13.82$) in the early adolescent group; however, this difference was only marginally significant [$t(45) = 1.77$, $p = 0.08$]. Higher PPVT scores among the early adolescents correlated significantly with their inclusion of a greater proportion of LP chapters ($r = 0.30$, $p < 0.05$); there were no associations between PPVT and any of the life story variables for the middle childhood group.

Main analyses

Each participant had separate scores for the number of chapters, LP chapters, SE chapters, and chapters with specific memories. Raw scores were then converted into proportions of the total number of chapters (see **Table 1**). There were no significant age or gender differences in the number of chapters or the number of chapters containing specific memories, nor were there any interactions between gender and age on the different components of life story chapters.

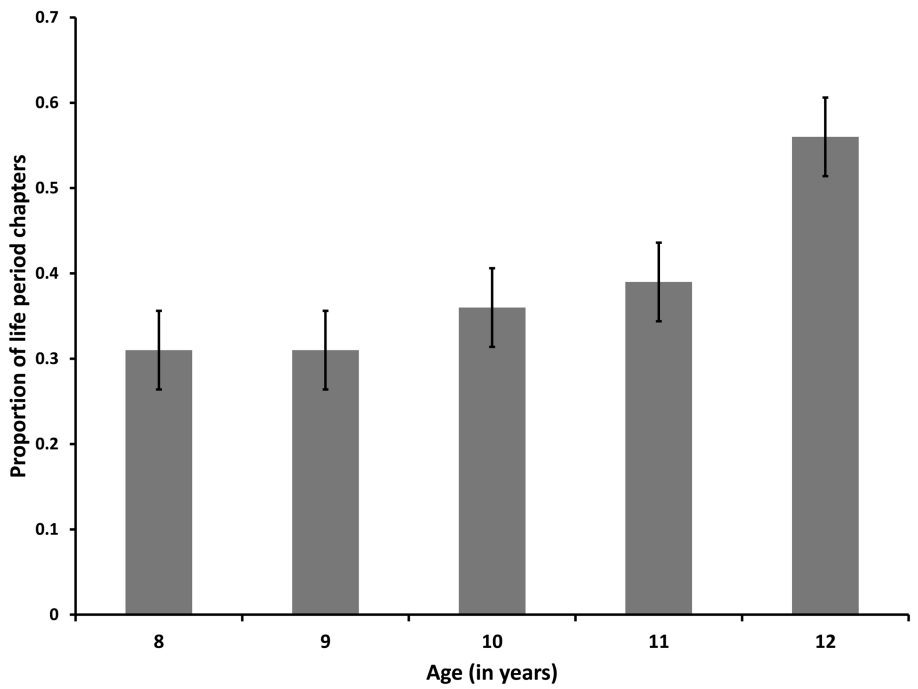


FIGURE 1 | Proportions of lifetime-period chapters across age groups (Study 1).

Table 1 | Number and types of life story chapters in middle childhood and early adolescence (Study 1).

Chapter task variables	Middle childhood ($N = 76$)		Early adolescence ($N = 48$)	
	M	SD	*M*	SD
Number of chapters	5.68	2.33	6.00	2.20
Proportion of LP chapters[a]	0.33	0.34	0.48	0.38
Number of SPE chapters[b]	4.75	2.46	4.67	2.18

[a] *Proportion of lifetime-period chapters.*

[b] *Number of chapters containing specific memories.*

Analyses of variance (ANOVAs) were conducted to test the effects of age and gender on the structure of life story chapters. LP and SE chapters were coded with a mutually exclusive scheme, and consequently, these codes yielded the same results (but with findings in the opposite direction). As PPVT was correlated with this variable, an ANCOVA was also conducted to test the effects of age and gender on the proportion of LP chapters when controlling for PPVT. In the interests of brevity, we only report the results for LP chapters; it can be assumed that the inverse finding was present for SE chapters.

The results showed a main effect of age on the proportion of LP chapters, such that children in the middle childhood group had smaller proportions of LP chapters in their life stories than did those in the early adolescence group [$F(1, 120) = 4.99$, $p = 0.03$, partial $\eta^2 = 0.04$]. There was also a main effect of gender, with girls reporting higher proportions of LP chapters ($M = 0.46$, $SD = 0.35$) than boys ($M = 0.30$, $SD = 0.36$), $F(1, 120) = 4.53$, $p = 0.04$, partial $\eta^2 = 0.04$. This effect remained the same when controlling for PPVT.

So far we have shown that the ability to organize autobiographical memories based on lifetime periods emerges late in middle childhood. Thus, the hierarchical structure of autobiographical memories (i.e., the integration of episodic memory and autobiographical knowledge base) begins to establish in this age range. Previous research has investigated the development of autobiographical memory in middle childhood and early adolescence in terms of autonoesis (e.g., Piolino et al., 2007) and age-related differences between episodic and semantic autobiographical memories (e.g., Willoughby et al., 2012). To our knowledge, however, Study 1 is the first to provide evidence on the developmental trajectory of the organization of episodic memory in middle childhood and early adolescence.

Given the findings so far, we wanted to explore how memory structure continues to develop beyond early adolescence in Study 2. Furthermore, given previous findings on cultural differences in the content of episodic memories (e.g., MacDonald et al., 2000; Wang, 2006a, 2008), we wanted to determine whether the organization and structure of episodic memories also differs between NZE and NZC adolescents.

STUDY 2

METHOD

Participants

One hundred and seventy-eight adolescents (96 females, 82 males) aged between 12 and 21 years ($M = 16.92$ years, $SD = 2.52$) took part in Study 2. All participants were part of a larger research project on identity development in adolescence (see Chen et al., 2012 for further details). Participants above the age of 18 were recruited from the local university and through a student employment agency. The remainder of the participants was recruited from secondary schools in two towns and one city in New Zealand. All participants identified themselves as either European New Zealanders (NZE, $N = 90$) or as first- or second-generation immigrants with Chinese ancestry (NZC, $N = 88$). Seventy-six NZE and 37 NZC adolescents were born in New Zealand, and 80% of adolescents who were born overseas (8 NZE and 41 NZC) had spent more than 5 years living in New Zealand.

Based on social and educational milestones (i.e., starting high school at age 12 or 13, getting a driver license at age 15, finishing high school, and being eligible to vote at age 18), combined with theoretical claims that the life story develops rapidly in mid to late adolescence, adolescents in Study 2 were divided into three age groups. The early adolescent group consisted of adolescents between the ages of 12 and 14 (24 girls and 25 boys), the mid-adolescent group consisted of those aged between 15 and 17 years old (37 girls and 26 boys), and the late adolescent group consisted of students aged between 18 and 21 (36 girls and 30 boys).

All participants gave their consent before being interviewed, and parental consent was also obtained for those who were younger than 16 years old at the time of the interview. One of the interviewers was bilingual (Mandarin Chinese and English) so participants could chose the language they were interviewed in; participants in this research all chose to speak in English. Among NZC adolescents who were born outside of New Zealand, the mean length of residency in New Zealand was 5.55 years. There were no differences in the number of years that they had lived in New Zealand by age group [$F(2, 48) = 1.15$, $p > 0.05$]. Similar to Study 1, participants' life story chapters were coded based on the interviewer's record of story structure and content.

Procedure

The interview started with the life story task, which was very similar to the procedure carried out in Study 1. However, participants were encouraged to keep the number of chapters they narrated to seven. We decided on this number based on findings from Study 1 that about 80% of children provided seven or fewer chapters, and also on McAdams' (1995) life story interview procedure. Seven chapters provided adolescents with enough space to convey the important events that happened in their lives, but constrained the time burden of the overall interview.

As in Study 1, the narrator was told to start with the chapter that she/he was in right now and to narrate backwards to the first chapter. The interviewer did not give any specific instructions on the content of the chapters. Once the narrator had reached the first chapter, the interviewer recapped all the chapters in a chronological order as in Study 1, so that the narrator had a chance to verify the content or add new information to the life story.

Coding

Coding of chapter tasks for lifetime periods and for specific memories was conducted in the same fashion as Study 1. Reliability was calculated based on 25% of the total transcripts, with an equal number of transcripts from both cultures. Percentage agreement

was calculated in the same fashion as in Study 1 and ranged from 94 to 100% agreement. The remaining transcripts were coded by the main coder.

RESULTS

Multivariate analysis of variance (MANOVA) was conducted to test the effects of gender, culture, and age on the structure of life story chapters in adolescence (see **Table 2** for descriptives). Significant multivariate effects were followed up by univariate analyses. There were no significant gender differences for any of the variables related to the structure of the life story. A main effect of culture was found for the number of chapters [$F(1, 166) = 27.35$, $p < 0.001$, partial $\eta^2 = 0.14$]; NZE adolescents included more life story chapters than their NZC counterparts. This main effect was further qualified by an interaction between culture and age [$F(2, 166) = 5.70$, $p < 0.05$, partial $\eta^2 = 0.06$]; NZE adolescents in the two younger age groups (e.g., early and mid-adolescence) had more chapters than did their NZC counterparts [$t(47) = 4.50$ and $t(61) = 2.64$, respectively, $ps < 0.05$]. However, these cultural differences were not present for the late adolescence group. A main effect of culture was also found for the number of chapters with specific memories [$F(1, 166) = 7.67$, $p < 0.05$, partial $\eta^2 = 0.04$], such that NZE adolescents had more chapters with specific memories ($M = 2.49$, SD = 2.00) than did NZC adolescents ($M = 1.74$, SD = 1.43). There were no cultural differences when comparing the proportion of LP chapters and the number of chapters with specific memories.

However, there were age-related differences in the proportion of LP chapters [$F(2, 166) = 5.41$, $p < 0.05$, partial $\eta^2 = 0.06$]. *Post hoc* Bonferroni tests showed that the significant difference for the proportion of LP chapters was found between the early ($M = 0.94$, SD = 0.14) and the late adolescent group ($M = 1.00$, SD = 0), such that no-one above the age of 18 organized their life story with SE chapters.

DISCUSSION

The self-memory system theory (Conway and Pleydell-Pearce, 2000; Conway, 2005, 2009) claims that autobiographical memory is constructed in a hierarchy, which consists of episodic memories at the lowest level, general events and lifetime periods in the middle, and the life story at the highest level. Our studies investigated the development of this hierarchy from middle childhood to young adulthood by comparing the ability to use lifetime periods, as opposed to single events, as a means of organizing the life story – the most abstract structure of autobiographical memory – among 8- to 21-year-olds. In Study 1, the proportion of LP chapters in the life story increased from middle childhood to early adolescence in participants of NZE descent. In Study 2, we compared the structure of the life story between NZE and NZC adolescents aged between 12 and 21. Regardless of ethnicity, the use of LP chapters continued to increase with age, suggesting that the use of lifetime periods is still developing past age 12. By age 18, all participants organized the life story based on lifetime periods. This similarity in the organization of life stories across cultures contrasts with past findings of cultural differences in the content of autobiographical memories (Wang, 2006a). However, in line with that literature, NZC adolescents had fewer life story chapters, and fewer chapters containing specific memories, than did NZE adolescents. This finding is consistent with Wang (2009a), in which Asian participants recalled fictional stories in fewer segments than their American European counterparts.

The current studies suggest that the ability to organize episodic memories in terms of lifetime periods is generally mastered by mid-adolescence for NZE and NZC adolescents, but continues to develop in a similar fashion into late adolescence for both cultures. Moreover, despite cultural similarities in this organizational structure, culture-related differences in the volume of memories were still present in terms of the number of life story chapters and the inclusion of specific memories within those chapters. It appears that these cultural differences are in the specificity and in the quantity of memories but not in the organization of those memories.

THE CONTINUED DEVELOPMENT OF EPISODIC MEMORY IN ADOLESCENCE

Children as young as 3 years old are capable of recalling specific episodic memories (Scarf et al., 2013). By the time they reach middle childhood, most children can recall autobiographical

Table 2 | Number and types of life story chapters in early, mid, and late adolescence as a function of culture (Study 2).

	Early adolescence		Mid-adolescence		Late adolescence	
	M	**SD**	***M***	**SD**	***M***	**SD**
NZE	($N = 29$)		($N = 31$)		($N = 30$)	
Number of chapters	5.34	2.09	4.52	1.69	4.67	1.35
Proportion of LP chapters[a]	0.92	0.16	0.95	0.13	1.00	–
Number of SPE chapters[b]	2.76	2.37	2.45	1.73	2.27	1.91
NZC	($N = 20$)		($N = 32$)		($N = 36$)	
Number of chapters	3.1	0.91	3.56	1.13	4.28	1.03
Proportion of LP chapters[a]	0.96	0.12	0.99	0.04	1.00	–
Number of SPE chapters[b]	1.60	1.39	1.44	1.29	2.08	1.50

[a] *Proportion of lifetime-period chapters.*

[b] *Number of chapters containing specific memories.*

memories with detailed descriptions of the *what, when, where* of the events, as well as an enriched account of emotional elaborations and self reflections (e.g., Fivush et al., 2003, 2008; Piolino et al., 2007). Although the ability to recall specific details of personal experiences in an adult-like fashion may be present in middle childhood, the organization of episodic memories in the life story is still developing in middle childhood and adolescence. Note that in Study 2, children in the early adolescent group reported higher proportions of LP chapters compared to the early adolescent group in Study 1. This is most likely due to the fact that the early adolescent group in Study 2 was older on average ($M = 13.6$ years) than in Study 1 ($M = 12.1$ years). Our findings suggest that the years from 8 to 14 are particularly important for the ability to use abstract structures (such as lifetime periods and general events) to organize long-term memory. Without specific instructions, older adults automatically use lifetime periods as the basic units to organize chapters of the life story (Thomsen, 2009).

In contrast, we prompted children and adolescents to tell a life story based on chapters, and found age-related differences in the structure of those chapters. We observed an increase in the use of LP chapters and a decrease in the use of SE chapters with age. By the time they reached late adolescence, all of their life stories were based on lifetime periods. Gaining an understanding of the overarching themes of a life story may help adolescents to understand what a life story should look like and help them to organize their stories in an adult-like fashion.

CULTURE, AUTOBIOGRAPHICAL MEMORY, AND THE LIFE STORY

Cultural differences based on the content of autobiographical memory also extended to the structure of the life story. We found that NZC adolescents had fewer life story chapters compared to NZE adolescents up to the age of 18. This is consistent with the interpretation that people from Eastern cultures tend to use a holistic approach in memory encoding, such that they focus on the connections among events and recall them as general events (Nisbett and Miyamoto, 2005).

Furthermore, cultural differences in memory specificity (Wang, 2009b; Wang et al., 2011) were also shown in the content of life story chapters in Study 2. Regardless of age, NZC adolescents had fewer chapters containing specific memories than did NZE adolescents. Given this study was exploratory, further research is needed to determine what, if any, effects these cultural disparities have on aspects of the self-memory system and the self. For example, what are the consequences of having general versus specific memories as the basic elements of the life story? Would this cultural disparity in memory structure have implications for the self concept (e.g., Wang, 2008)?

Although it does appear in Study 1 that girls have a head start in organizing their memories in middle childhood, these gender differences are not apparent in adolescence. In Study 2, there were no gender differences in any of the variables relating to life story organization for any of the age groups for either culture. Willoughby et al. (2012) found that girls between the ages of 8 and 16 reported more episodic autobiographical memories than boys, and Wang et al. (in press) found similar results in a younger sample of European Americans, although this gender difference was not present among a sample of Chinese immigrants. Our findings indicate a lack of gender differences in both NZE and NZC adolescents. Thus it appears that there are some inconsistencies in the literature with regard to whether gender influences the specificity of autobiographical memories. It may be that gender differences are culturally determined, rather than common across cultures.

STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

The current paper provides the first developmental evidence to support the claims of the self-memory system theory that autobiographical memories can be organized in terms of the life story, lifetime periods, and episodic memories. However, we were not able to elaborate on some memory components (i.e., general events and mini-narratives) within the self-memory system framework as our coding was based on an outline of the life story, consisting of titles of story chapters and keywords for the events. Future studies could incorporate the whole range of memory structures that are included in the life story. In line with Conway's (2009) theory, we would predict that including general events would serve as an intermediary step in organizing episodic memories prior to the use of lifetime periods. We also showed that although there were some differences in the length and specificity of life stories between NZE and NZC adolescents, the organization of episodic memory developed in similar ways across the two groups. Because cultural differences in memory specificity were attenuated with age, there is a possibility that the mature self-memory system captures a memory organization that is shared across cultures. Moreover, Study 2 was based on comparisons between a sample of immigrants and their host nation; the cross-cultural differences might have been reduced due to cultural assimilation of the immigrants (Wang, 2006b). Further studies are required to compare the structure of autobiographical memories between cultures that are geographically independent in order to continue to investigate the cross-cultural validity of the self-memory system model.

Furthermore, past research has shown that the content of life story chapters is associated with cultural life scripts, which contain knowledge about the type and timing of typical events that should occur in one's life (Thomsen and Berntsen, 2008). Future studies could examine whether acquisition of a cultural life script precedes the ability to use lifetime periods to organize episodic memories.

CONCLUSION

Our studies showed that the ability to organize episodic memories based on lifetime periods develops significantly from middle childhood to mid-adolescence. This finding supports Conway's (2009) theory of the hierarchical nature of the autobiographical knowledge base. Moreover, this finding extends Conway's theory to show that episodic memories precede and support the development of higher-order structures in the autobiographical knowledge base in the form of lifetime periods (see Conway, 2009, Figure 2). This cognitive development may be the precursor to adolescents' ability to find overarching themes from discrete episodic memories. That is, this organization may be related to the ability to narrate life stories that are integrated with respect to time and place during mid- and late adolescence (Habermas and de Silveira, 2008).

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REFERENCES

Chen, Y., McAnally, H. M., Wang, Q., and Reese, E. (2012). The coherence of critical event narratives and adolescents' psychological functioning. *Memory* 20, 667–681. doi:10.1080/09658211.2012.693934

Conway, M., Singer, J. A., and Tagini, A. (2004). The self and autobiographical memory: correspondence and coherence. *Soc. Cogn.* 22, 495–537. doi:10.1521/soco.22.5.491.50768

Conway, M. A. (2005). Memory and the self. *J. Mem. Lang.* 53, 594–628. doi:10.1016/j.jml.2005.08.005

Conway, M. A. (2009). Episodic memories. *Neuropsychologia* 47, 2305–2313. doi:10.1016/j.neuropsychologia.2009.02.003

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–288. doi:10.1037/0033-295x.107.2.261

Dunn, L. M., and Dunn, L. M. (2007). *Peabody Picture Vocabulary Test, 4th Edn.*, Minneapolis, MN: NCS Pearson, Inc.

Elley, W. B., and Irving, J. C. (2003). The elley-irving socio-economic index: 2001 census revision. *New Zeal. J. Educ. Stud.* 38, 3–17.

Fivush, R., Hazzard, A., Sales, J. M., Sarfati, D., and Brown, T. (2003). Creating coherence out of chaos? Children's narratives of emotionally positive and negative events. *Appl. Cogn. Psychol.* 17, 1–19. doi:10.1002/Acp.854

Fivush, R., McDermott Sales, J., and Bohanek, J. G. (2008). Meaning making in mothers' and children's narratives of emotional events. *Memory* 16, 579–594. doi:10.1080/09658210802150681

Fivush, R., and Nelson, K. (2004). Culture and language in the emergence of autobiographical memory. *Psychol. Sci.* 15, 573–577. doi:10.1111/j.0956-7976.2004.00722.x

Fivush, R., and Wang, Q. (2005). Emotion talk in mother-child conversations of the shared past: the effects of culture, gender, and event valence. *J. Cogn. Dev.* 6, 489–506. doi:10.1207/s15327647jcd0604_3

Friedman, W. J., Reese, E., and Dai, X. (2011). Children's memory for the times of events from the past years. *Appl. Cogn. Psychol.* 25, 156–165. doi:10.1002/acp.1656

Habermas, T., and Bluck, S. (2000). Getting a life: the development of the life story in adolescence. *Psychol. Bull.* 126, 748–769. doi:10.1037/0033-2909.126.5.748

Habermas, T., and de Silveira, C. (2008). The development of global coherence in life narratives across adolescence: temporal, causal, and thematic aspects. *Dev. Psychol.* 44, 707–721. doi:10.1037/0012-1649.44.3.707

Howe, M. L., and Courage, M. L. (1993). On resolving the enigma of infantile amnesia. *Psychol. Bull.* 113, 305–326. doi:10.1037//0033-2909.113.2.305

Howe, M. L., and Courage, M. L. (1997). The emergence and early development of autobiographical memory. *Psychol. Rev.* 104, 499–523. doi:10.1037//0033-295X.104.3.499

Kulkofsky, S., Wang, Q., and Koh, J. B. K. (2009). Functions of memory sharing and mother-child reminiscing behaviors: individual and cultural variations. *J. Cogn. Dev.* 10, 92–114. doi:10.1080/15248370903041231

MacDonald, S., Uesiliana, K., and Hayne, H. (2000). Cross-cultural and gender differences in childhood amnesia. *Memory* 8, 365–376. doi:10.1080/09658210050156822

Markus, H. R., and Kitayama, S. (1991). Culture and the self: implications for cognition, emotion, and motivation. *Psychol. Rev.* 98, 224–253. doi:10.1037//0033-295X.98.2.224

McAdams, D. P. (1995). *The Life Story Interview*. Available at: http://www.sesp.northwestern.edu/foley/instruments/interview

McAdams, D. P. (1996). Personality, modernity, and the storied self: a contemporary framework for studying persons. *Psychol. Inq.* 7, 295–321. doi:10.1207/s15327965pli0704_1

Mullen, M. K. (1994). Earliest recollections of childhood: a demographic analysis. *Cognition* 52, 55–79. doi:10.1016/0010-0277(94)90004-3

Mullen, M. K., and Yi, S. (1995). The cultural context of talk about the past: implications for the development of autobiographical memory. *Cogn. Dev.* 10, 407–419. doi:10.1016/0885-2014(95)90004-7

Nelson, K., and Fivush, R. (2004). The emergence of autobiographical memory: a social cultural developmental theory. *Psychol. Rev.* 111, 486–511. doi:10.1037/0033-295x.111.2.486

Nisbett, R. E., and Miyamoto, Y. (2005). The influence of culture: holistic versus analytic perception. *Trends Cogn. Sci. (Regul. Ed.)* 9, 467–473. doi:10.1016/j.tics.2005.08.004

Perner, J. (2001). "Episodic memory: essential distinctions and developmental implications," in *The Self in Time: Developmental Perspectives*, eds C. Moore and K. Lemmon (Mahwah, NJ: Lawrence Erlbaum Associates), 181–202.

Perner, J., and Ruffman, T. (1995). Episodic memory and autonoetic consciousness: developmental evidence and a theory of childhood amnesia. *J. Exp. Child. Psychol.* 59, 516–548. doi:10.1006/jecp.1995.1024

Piolino, P., Hisland, M., Ruffeveille, I., Matuszewski, V., Jambaqué, I., and Eustache, F. (2007). Do school-age children remember or know the personal past? *Conscious. Cogn.* 16, 84–101. doi:10.1016/j.concog.2005.09.010

Reese, E. (2002). Social factors in the development of autobiographical memory: the state of the art. *Soc. Dev.* 11, 124–142. doi:10.1111/1467-9507.00190

Reese, E., Chen, Y., Jack, F., and Hayne, H. (2010). "Emerging identities: narrative and self from early childhood to early adolescence," in *Narrative Development in Adolescence: Creating the Storied Self*, eds K. C. McLean and M. Pasupathi (New York, NY: Springer), 23–44.

Scarf, D., Gross, J., Colombo, M., and Hayne, H. (2013). To have and to hold: episodic memory in 3- and 4-year-old children. *Dev. Psychobiol.* 55, 125–132. doi:10.1002/dev.21004

Smith, T. C., Smith, B. L., and Dobbs, K. (1991). Relationship between the peabody picture vocabulary test-revised, wide range achievement test-revised, and Weschler intelligence scale for children-revised. *J. Sch. Psychol.* 29, 53–56. doi:10.1016/0022-4405(91)90015-J

Thomsen, D. K. (2009). There is more to life stories than memories. *Memory* 17, 445–457. doi:10.1080/09658210902740878

Thomsen, D. K., and Berntsen, D. (2008). The cultural life script and life story chapters contribute to the reminiscence bump. *Memory* 16, 420–435. doi:10.1080/09658210802010497

Thomsen, D. K., Pillemer, D. B., and Ivcevic, Z. (2011). Life story chapters, specific memories and the reminiscence bump. *Memory* 19, 267–279. doi:10.1080/09658211.2011.558513

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi:10.1037/h0080017

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Tulving, E. (2005). "Episodic memory and autonoesis: uniquely human?," in *The Missing Link in Cognition: Origins of Self-Reflective Consciousness*, eds H. S. Terrace and J. Metcalfe (New York: Oxford University Press), 3–56.

Wang, Q. (2006a). Earliest recollections of self and others in European American and Taiwanese young adults. *Psychol. Sci.* 17, 708–714. doi:10.1111/j.1467-9280.2006.01770.x

Wang, Q. (2006b). Relations of maternal style and child self-concept to autobiographical memories in Chinese, Chinese immigrant, and European American 3-year-olds. *Child Dev.* 77, 1794–1809. doi:10.1111/j.1467-8624.2006.00974.x

Wang, Q. (2008). Being American, being Asian: the bicultural self and autobiographical memory in Asian Americans. *Cognition* 107, 743–751. doi:10.1016/j.cognition.2007.08.005

Wang, Q. (2009a). Are Asians forgetful? Perception, retention, and recall in episodic remembering. *Cognition* 111, 123–131. doi:10.1016/j.cognition.2009.01.004

Wang, Q. (2009b). Once upon a time: explaining cultural differences in episodic specificity. *Soc. Personal. Psychol. Compass.* 3, 413–432. doi:10.1111/j.1751-9004.2009.00182.x

Wang, Q., Capous, D., Kim Koh, J. B., and Hou, Y. (in press). Past and future episodic thinking in middle childhood. *J. Cogn. Dev*. doi:10.1080/15248372.2013.784977

Wang, Q., Hou, Y., Tang, H., and Wiprovnick, A. (2011). Travelling backwards and forwards in time: culture and gender in the episodic specificity of past and future events. *Memory* 19, 103–109. doi:10.1080/09658211.2010.537279

Wheeler, M. A., Stuss, D. T., and Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychol. Bull.* 121, 331–354. doi:10.1037//0033-2909.121.3.331

Willoughby, K. A., Desrocher, M., Levine, B., and Rovet, J. F. (2012). Episodic and semantic autobiographical memory and everyday memory during late childhood and early adolescence. *Front. Psychol.* 3:53. doi:10.3389/fpsyg.2012.00053

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The influence of prior knowledge on memory: a developmental cognitive neuroscience perspective

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Across ontogenetic development, individuals gather manifold experiences during which they detect regularities in their environment and thereby accumulate knowledge. This knowledge is used to guide behavior, make predictions, and acquire further new knowledge. In this review, we discuss the influence of prior knowledge on memory from both the psychology and the emerging cognitive neuroscience literature and provide a developmental perspective on this topic. Recent neuroscience findings point to a prominent role of the medial prefrontal cortex (mPFC) and of the hippocampus (HC) in the emergence of prior knowledge and in its application during the processes of successful memory encoding, consolidation, and retrieval. We take the lateral PFC into consideration as well and discuss changes in both medial and lateral PFC and HC across development and postulate how these may be related to the development of the use of prior knowledge for remembering. For future direction, we argue that, to measure age differential effects of prior knowledge on memory, it is necessary to distinguish the availability of prior knowledge from its accessibility and use.

Keywords: lifespan development, child development, hippocampus, medial prefrontal cortex, semantic memory, prior knowledge, lateral prefrontal cortex, episodic memory

INTRODUCTION

As humans, we do not store verbatim copies of experiences in our memory. Rather, we integrate new incoming information from the surroundings in relation to our pre-existing knowledge about the world. This knowledge is accumulated across ontogenetic development through experiences during which the individual detects regularities in the environment. Growth in knowledge is one of the most prominent aspects in ontogeny and exerts its influence on memory functioning across the whole lifespan (Craik and Bialystok, 2006). The importance of prior knowledge for memory has been introduced in the classical work of Piaget (1929) and Bartlett (1932). Bartlett (1932) showed that humans, while recalling a specific event, often construct these memories based on their knowledge about the world, thus illustrating the susceptibility of human memories to errors due to their reconstructive nature. In his work with children, Piaget (1929) showed that, in addition to the assimilation of new information into existing knowledge frames (or schemata), knowledge has to be updated frequently in order to adapt to changing demands of the environment, a process he called accommodation. Despite the long-standing recognition of the important role of prior knowledge, most psychological and cognitive neuroscience experiments are designed with the implicit assumption that learning and memory take place in a tabula rasa state of the brain. So far, surprisingly little is known about how the interaction between pre-existing knowledge and new incoming information takes place within the brain.

In the following sections, we discuss both behavioral and neuroscience findings concerning the influence of prior knowledge on memory. We focus on studies that examined long-term storage of memory, as prior knowledge directly influences cognitive processes that are important for learning and retaining new information in the memory system. The representations built up from these processes form the basis of semantic memory, which is factual knowledge about the world, and episodic memory, which is memory bound in time and place (Tulving, 1972). In the remainder of the review, we outline a developmental cognitive neuroscience perspective that combines our understanding about changes in brain structure and function across development with behavioral findings of age differences in the use of prior knowledge for remembering. This developmental cognitive neuroscience perspective shall guide future investigations of age-related changes in the use of prior knowledge for remembering in brain and behavior simultaneously. Throughout the review, we use the term prior knowledge in a broad sense as stored knowledge and beliefs about the world that have been acquired by an individual. This knowledge can be declarative (i.e., semantic, episodic) or non-declarative (e.g., implicit or procedural). We hereby acknowledge that differences among related terms such as conceptual knowledge, rule knowledge, associative knowledge, and schema are not being considered.

BEHAVIORAL EVIDENCE ILLUSTRATING THE INFLUENCE OF PRIOR KNOWLEDGE ON MEMORY

In a classical study, Bransford and Johnson (1972) demonstrated the impact of prior knowledge on comprehension and memory. In a series of experiments, participants were asked to listen to prose passages and were afterward tested on their memory for them. Participants who received relevant knowledge or cues before listening to the passages and therefore had prior knowledge available showed improved comprehension and better recall compared to

participants who either did not receive cues or received the contextual knowledge only after hearing the passages. In a second experiment, Bransford and Johnson (1972) used descriptions of activities that were known to the participants. They manipulated whether the participants could access this knowledge by either providing or not providing a cue that allowed the activation of an appropriate context. As expected, comprehension and recall were better for the group that received the cue beforehand as compared to the no-cue group. In sum, the results indicate that if prior knowledge is available and accessible, it facilitates comprehension and memory of new incoming information. Moreover, these findings corroborate the view that our experiences are not remembered as exact copies, but are actively integrated into one's existing knowledge structures.

In a similar vein, Craik and Lockhart (1972) argued that memory performance is not a simple function of the amount of encoded features (that is, the more, the better), but also of the qualitative nature of these features, i.e., how well they can be integrated into pre-existing knowledge. For example, Craik and Tulving (1975) demonstrated that words that were embedded in a congruent sentence context were better remembered than those that were embedded in an incongruent context (see also Schulman, 1974). In addition to showing a general benefit for congruously encoded items, Craik and Tulving (1975) also showed that a semantically rich context benefits memory for congruent words but does not affect memory for incongruent words. These results were taken to implicate a more elaborative encoding for congruent as opposed to incongruent information. Also, new information is more effectively integrated into existing semantic networks when presented stimulus and context form one unit. Since Craik and Tulving (1975), this so-called "congruency effect" has been replicated numerous times with different stimulus materials and tasks (e.g., Staresina et al., 2009; for a review, see Alba and Hasher, 1983).

Following the initial idea that prior knowledge benefits encoding via integration into existing semantic structures, Moscovitch and Craik (1976) provided a retrieval-related view on the importance of semantic context. In an incidental encoding task, participants read words on a screen and were asked to indicate whether those words either rhyme with another word, fit into a given category, or fit into a given sentence. The latter task was assumed to provide the deepest level of encoding. In addition, they manipulated retrieval conditions by irregularly presenting the initial encoding questions once more that did (yes-answers) or did not (no-answers) form a congruent unit with the target word. They showed that both cueing and congruency at retrieval enhanced recall and that this worked best in combination with deep levels of encoding. The results led the authors to postulate that recall performance depends on three factors: the quality of the trace (defined by the level of processing), the presence of retrieval cues, and the degree of congruity of the items with their context. Put differently, deep encoding comes along with a high potential of being remembered. The extent to which this potential is realized, however, depends on whether the retrieval context provides enough information to recreate the encoding context and on whether this context and the target stimulus form one unit. When all (or some) conditions are met, the retrieval of accurate targets will be facilitated.

Although it is well accepted that semantic congruency promotes memory performance, events that are incongruent to the prevailing context have also been shown to-be-remembered well. For example, the classical von Restorff-effect (Köhler and von Restorff, 1937) denotes that an item that is distinct from its surrounding items is more likely to-be-remembered than one that is not (also called "isolation effect"). Whether a given memory event profits from congruency or incongruency probably depends on several contextual features, such as the occurrence ratio between congruent and incongruent information (Alba and Hasher, 1983; Rojahn and Pettigrew, 1992). By taking a 50/50 ratio of congruent and incongruent stimuli, differences in saliency are reduced, which would be more prominent for, say, an 80/20 ratio in which the less frequent material type is expected to show isolation-like memory benefits (Hunt and Lamb, 2001).

However, explaining effects of distinctiveness with saliency or isolation alone is not sufficient. One intuitive mechanism through which distinctiveness operates is the effect of increased attention to the salient item, which is sparked by, for example, an emotional response to salience or surprise (Hunt and Lamb, 2001). Contrary to this explanation, it was shown that subjectively perceived salience is not necessary for the isolation effect (Dunlosky et al., 2000). Alternatively, distinctiveness can be understood as "the processing of difference in the context of similarity" (Hunt and Lamb, 2001). This implies that distinctiveness is not a property of the physical objects, but a certain kind of cognitive processing that creates more elaborate traces for isolated items. Accordingly, the end product of distinctive processing is an elaborate memory trace that is highly unique and easy to access during retrieval. Although this notion focuses on memory benefits due to the incongruity of an event, it is consistent with the general notion of the levels-of-processing account stating that remembering depends on the degree of elaboration of a trace during encoding in relation to existing knowledge structures (Craik and Lockhart, 1972).

CONCLUSION REGARDING BEHAVIORAL DATA

Prior knowledge facilitates processing of new incoming information, supposedly because it provides a structure into which the new information can be integrated, which may lead to an elaborated memory trace. This advantage of prior knowledge may hold, no matter if the new information meets expectations (is congruent with existing knowledge) or not (is incongruent). However, having prior knowledge available does not suffice, it needs to be accessed and used to benefit encoding (Bransford and Johnson, 1972; Alba and Hasher, 1983). Moreover, an elaborated memory trace only provides potential for later remembering. The extent to which this potential is realized might then depend on whether the retrieval context matches the encoding context to a certain degree and on whether it is distinct enough to activate the specific target trace. This suggests that it is necessary to look at retrieval as well in order to understand the memory benefit for elaborated information.

During retrieval, semantic knowledge might help to reinstate the encoding context, which was shown to be facilitated if the item is expected to occur in the specific context based upon prior knowledge (Moscovitch and Craik, 1976). From a spreading activation network perspective, an existing semantic structure provides a search space that is likely to contain additional routes by which the

new information can be inferred if direct retrieval fails (Anderson, 1981). This may also be true if the item posits a mismatch with the context, as the degree of distinctiveness or novelty can also be diagnostic at retrieval. From a neuroscience point of view, however, only little is known about how these computations are carried out in the brain. In the next section, we will review recent neuroscience findings concerning the processing of information related to prior knowledge, particularly during memory processing.

A NEUROIMAGING VIEW ON THE CONNECTION BETWEEN PRIOR KNOWLEDGE AND MEMORY

This section will first offer an overview over initial evidence suggesting the involvement of the medial temporal lobe [(MTL), especially the hippocampus (HC)] and PFC structures in the coordination of forming and applying knowledge. Based on this, we will examine the roles of MTL and PFC in making use of prior knowledge for the service of memory encoding, consolidation, as well as retrieval. A large part of this section will deal with medial prefrontal cortex (mPFC) and HC, as recent evidence and theorizing suggest both areas to be key regions for understanding the interplay between knowledge and memory functions. In addition, we will discuss the involvement of lateral PFC subregions. The latter provide important control and elaborative functions with regard to accessing and evaluating internal mnemonic representations.

The hippocampal formation forms part of the MTL and is a set of cortical regions comprising the dentate gyrus (DG) and the individual CA-fields in the HC as well as the subicular complex. The entorhinal cortex, perirhinal cortex, as well as the parahippocampal cortex, which all surround the HC, also play a role in the functioning of memory as they are the primary sources of neocortical inputs to the HC (Squire, 1992; Andersen et al., 2007). Regarding subregions of the mPFC that are presumably relevant to prior knowledge, we refer to Brodmann areas (BA) 12 and 25, the ventral parts of BA 32, and the medial parts of BA 10 and BA 11. Taken together, those subregions are similar to the subgenual ventromedial PFC (vmPFC) as defined by Nieuwenhuis and Takashima (2011), but also include anterior and dorsal parts of BA 10. There is a broad literature about mPFC function and anatomy in rodents. However, as this is not the main focus of the present review, the interested reader might refer to Nieuwenhuis and Takashima (2011) for an overview and comparison with the human mPFC.

THE EMERGENCE OF KNOWLEDGE FROM THE COORDINATED INTERACTION BETWEEN mPFC AND HC

Both MTL and PFC play a crucial role in the emergence and application of abstract knowledge, as demonstrated by Kumaran et al. (2009). In this study, participants played the role of weather forecasters and had to learn which patterns of associative visual stimuli predicted sun or rain. This task could either be solved by learning the concrete surface pattern or by abstracting the commonalities across relevant patterns. The latter would supposedly lead to the emergence of conceptual knowledge that would allow transfer to new situations. The degree to which the participants acquired abstract knowledge was tested with a transfer task. Here the same higher-order task structure was used, but with different patterns of visual stimuli, thus making it necessary for the participants to reactivate the abstract conceptual representation acquired during the learning phase. The gradual acquisition of knowledge that allowed successful weather predictions was positively correlated with activation in the mPFC, HC, and posterior cingulate cortex. Moreover, better knowledge about the hierarchical structure was associated with an increased functional coupling between the HC and mPFC. The transfer task revealed correlations between transfer performance and neural activity in the left HC. A subsequent study by Kumaran et al. (2012) corroborated those initial observations. There, the authors explored the formation of knowledge of social and non-social hierarchies and its impact on the ability to perform transitive inference (e.g., if A > B and B > C, then A > C). Again, activity increases in the posterior HC and the mPFC paralleled the emergence of hierarchy knowledge, independent of it being a social or a non-social hierarchy (Kumaran et al., 2012).

The HC has traditionally been implicated in the creation and retrieval of enduring episodic memory traces (e.g., Simons and Spiers, 2003). Along this line, the role of specific HC-subfields (e.g., the DG) in the orthogonalization of representations of similar input patterns has been highlighted (i.e., pattern separation; McClelland et al., 1995). More recent studies also demonstrate HC involvement in inferential processing, such as flexibly combining memories to allow knowledge transfer (Zeithamova and Preston, 2010). Generalization across episodes might be supported via recurrent processing (i.e., pattern completion), either within specific HC-subfields (i.e., CA3/CA1; Marr, 1971; Treves and Rolls, 1992) or in larger HC-entorhinal cortex loops that act upon orthogonalized representations (for an in depth overview, see Kumaran and McClelland, 2012). Hence, a crucial facet of efficient HC processing resides in maintaining a fine balance between pattern separation and pattern completion operations (Yassa and Stark, 2011). These postulations still need to be validated by empirical evidence but might give a hint on how the HC is involved in constructing new abstract knowledge and how hippocampal computations may be susceptible to attentional modulation, possibly from the PFC (Duncan et al., 2009).

The mPFC, in turn, has traditionally been implicated in various functions including self-referential processing (e.g., Northoff and Bermpohl, 2004) and processing of reward-related information (e.g., Behrens et al., 2008). Given its involvement in reward processing, Kumaran et al. (2009) suggested that the mPFC may guide decision-making by integrating information received from the HC (discrete memories of encountering specific associative visual stimuli) with its associated value information (e.g., correctness of prediction, gain, and losses).

It is important to note that actual knowledge is probably not stored within the mPFC or the HC. In spite of the rich literature on representation of knowledge in the brain, we will limit ourselves to the statement that the storage of human knowledge corresponds to a network of parietal and temporal heteromodal association areas that receives input from multiple modalities (for review and meta-analysis, see Binder et al., 2009; Binder and Desai, 2011). HC and mPFC are suggested to form a network that builds up and integrates associative information with valuation, which then guides the acquisition of new conceptual knowledge (Kumaran et al., 2009). So far, the exact mechanisms through which the HC,

mPFC, and parietal/temporal association areas interact remain unclear.

In the subsequent section, we will discuss how the HC and the mPFC are involved in memory processes, starting with encoding and retrieval and followed by the consolidation of memories.

THE EFFECTS OF PRIOR KNOWLEDGE DURING MEMORY ENCODING: THE ROLES OF mPFC AND HIPPOCAMPUS

The initial findings by Bransford and Johnson (1972) that prior knowledge boosts comprehension and memory have been corroborated by neuroimaging work that tried to identify the neural correlates of this enhancement. An early PET-study (Maguire et al., 1999) adapted the paradigm of Bransford and Johnson (1972) by providing participants with relevant, irrelevant, or no visual cues before listening to stories in which the storyline was difficult to grasp. Maguire et al. (1999) revealed activations in the dorsal posterior cingulate area (PCC, BA 31) that was related to hearing the unusual passage when the helpful context picture was presented beforehand. Participants' ratings of the comprehensibility of the stories were positively correlated with activation in BA 31 and in ventral medial orbitofrontal cortex (BA 11) while activation in the left middle frontal gyrus (BA 10) was correlated with actual memory performance. These early findings emphasize the importance of prior knowledge for comprehension and memory by showing increased neural activations in medio-frontal regions (BA 10, BA 11) when knowledge is available during learning of new information.

More recent fMRI work examined effects of prior knowledge directly during episodic memory encoding. In a study by van Kesteren et al. (2010a), the availability of prior knowledge was manipulated by exposing two groups of participants to the first 80 min of a movie, either in correct (consistent schema) or scrambled order (inconsistent schema). On the next day's fMRI session, participants watched the movie's final 15 min in original order, after which they stayed in the scanner for an additional 15 min resting period (administered 10 min after encoding). Participants with an inconsistent schema showed higher correlations between HC- and mPFC-activity and less mPFC intersubject-synchronization, a measure of across-subject BOLD signal coherence. The higher correlation between HC and mPFC in the inconsistent schema group was interpreted as compensatory connectivity in order to make up for their lack of consistent schema. Interestingly, this increased correlation persisted during the 15 min post-encoding resting period, suggesting that a lack of prior knowledge could have resulted in increased spontaneous replay of the newly encoded information.

In a subsequent study, van Kesteren et al. (2013) assessed the influence of subjectively perceived congruency on mPFC and HC activation. In the MRI scanner, participants rated the congruency of object-scene pairs (e.g., classroom – chalk). About 24 h later outside of the scanner, they were tested on item and associative memory of the pairs. van Kesteren et al. (2013) examined the so-called subsequent memory effect, in which brain activations from encoding trials that resulted in subsequent remembering are directly contrasted with trials that are subsequently forgotten. The mPFC displayed an increase in the subsequent memory effect with congruency, whereas the left parahippocampal cortex showed a decrease with congruency in the subsequent memory effect. These findings support the notion that the mPFC plays a key role in the integration of new congruent information, whereas MTL areas are involved during the encoding of incongruent information (van Kesteren et al., 2012).

Taken together, initial evidence points to an involvement of mPFC and MTL regions during the encoding of new information that can be related to prior knowledge. In the next section, we will expand on these findings and examine the role of mPFC and HC in memory consolidation and retrieval.

THE INVOLVEMENT OF mPFC AND HC IN MEMORY CONSOLIDATION AND RETRIEVAL

The importance of prior knowledge for memory consolidation was emphasized in a recent review by Wang and Morris (2010). The authors argue that the brain stores associative frameworks of knowledge, which are supposedly implemented as networks of interconnected neocortical representations. The dynamic build-up of such structures is made possible by activity-dependent synaptic plasticity, as well as dendritic and synaptic growth. Hence, setting up such associative knowledge structures takes time. If these structures exist, however, the assimilation of related new information is expected to be facilitated, which would lead to speeded consolidation.

This reasoning is backed by studies with rats (Tse et al., 2007, 2011; McKenzie et al., 2013). Tse et al. (2007) showed that the removal of the entire HC as early as 48 h after the rapid learning of two new flavor-place associations fully spared memory when the rats were given extensive pre-training on six other flavor-place associations, i.e., prior knowledge. Consistently, rats that lacked prior knowledge displayed severe memory distortions after HC removal. These results suggest that neocortical sites are capable of rapid associative learning, if relevant prior knowledge is available. Moreover, in a subsequent study, Tse et al. (2011) provided evidence that the shift of the indexing function from the HC to the mPFC is not just a shift of locus, but rather a development through concurrent HC-mPFC interactions [see initial evidence for rapid memory consolidation in humans in Takashima et al. (2009)]. In addition, McKenzie et al. (2013) showed that neurons in the rat HC that were specific to certain trained goal locations in a circular track were initially active during the learning of new goals as well. As learning progressed, however, hippocampal activity patterns for old vs. new goal locations gradually diverged from one another. These findings were taken to suggest that consolidation involves both assimiliation of new information into existing knowledge structures and accommodation of these structures to ensure accurate memories, and that the HC plays a role in these processes.

In studies with human participants, tracking consolidation processes in the brain via the use of neuroimaging techniques has become increasingly prominent. Takashima et al. (2006) assessed changes in neural activation elicited by the retrieval of visual stimuli in a 3-month period after initial learning. Over the course of the entire study, participants showed a decrease in HC activation and an increase in mPFC-activity for confidently recognized pictures (see also Yamashita et al., 2009). These findings suggest that the mPFC takes over linking functions from the HC for retrieving coherent remote memories (see also Yamashita et al., 2009). This

reasoning is in accordance with an extended version of system consolidation theory, which states that, at first, the HC is necessary for storage and recovery of a memory trace. As consolidation proceeds, however, HC contributions diminish and cortical structures suffice to maintain the memory trace and to mediate its retrieval (Frankland and Bontempi, 2005; cf. Gais et al., 2007).

On the retrieval side, van Kesteren et al. (2010b) examined the neural underpinnings of the congruency effect during retrieval 24 h after learning in a visuo-tactile learning paradigm. Word-fabric combinations, which were either congruent or incongruent with common knowledge [e.g., the word "tie" was presented with a tie (congruent) or with a rubber (incongruent)] had to be associated with visual motifs. It was found that activity within the mPFC and the somatosensory cortex as well as the connectivity between the two areas was enhanced when motifs and associated words could be retrieved correctly. This was not the case when only the motifs were recognized without successful associative retrieval. Moreover, the increase in functional connectivity was positively correlated with the behavioral congruency benefit (i.e., more congruent hits than incongruent hits) associated with pre-existing knowledge across participants.

The finding of greater mPFC-activity for correctly remembered congruent motifs matches the supposed role of the mPFC in retrieval monitoring as providing a "feeling of rightness" for memory cues during retrieval. This monitoring function of the mPFC is assumed to bias later processing in the limbic system, including the HC (Moscovitch and Winocur, 2002). The existence of such a "feeling of rightness" is based on the compatibility of the memory cues with prior knowledge and is missing in confabulating patients with lesions in the mPFC (Gilboa et al., 2006). In line with this claim, in a recent review by Nieuwenhuis and Takashima (2011), it was argued that the mPFC integrates information from the limbic system and subsequently suppresses representations therein (especially in the HC) that might not be needed for retrieving information that fits prior knowledge. Based on this role of the mPFC, finding greater mPFC involvement during the retrieval of congruent compared to incongruent information seems conceivable, as only the former type of information elicits a "feeling of rightness." However, thus far the hypothesis of less hippocampal activation during the retrieval of congruent stimuli (due to suppression from mPFC) has not received empirical support. Hippocampal activity for congruent and incongruent stimuli did not differ during retrieval (van Kesteren et al., 2010b).

Thus far it appears that the neural structures mainly associated with system consolidation, i.e., MTL and mPFC, are also involved in the formation and application of abstract knowledge. This may not be a coincidence, as the effect of consolidation and the effect of knowledge abstraction, i.e., forming a conceptual "gist," resemble each other (cf. Ellenbogen et al., 2007). However, our remembering of remote episodes can certainly entail contextual details. In this case, evidence suggests that the HC remains involved (Nadel and Moscovitch, 1997).

LATERAL PFC CONTRIBUTIONS TO THE EFFECTS OF PRIOR KNOWLEDGE ON MEMORY

Despite the key role of the mPFC in recent literature on memory and knowledge, earlier studies have also demonstrated the involvement of lateral parts of the PFC (lPFC) in memory processes related to knowledge use, such as semantic elaboration (e.g., Kapur et al., 1994; Wagner et al., 1998) and relational processing of features contained in the to-be-remembered information (e.g., Fletcher et al., 2000; Addis and McAndrews, 2006; Murray and Ranganath, 2007). An early PET-study based on levels-of-processing ideas showed that elaborative encoding, as compared to shallow perceptual processing, goes along with increased activity in the left inferior frontal gyrus (Kapur et al., 1994). In line with that, Wagner et al. (1998) found that activations in the left lateral inferior frontal gyrus (together with left parahippocampal and fusiform gyri) was higher for subsequently remembered than for forgotten words. This finding indicates that elaborative processes involving the left inferior frontal gyrus directly benefit memory. Furthermore, a study that manipulated encoding through instructions to either remember or forget the preceding stimulus revealed that the condition in which participants had the intention to encode was linked to an increased activity in the left inferior frontal gyrus (Reber et al., 2002). Finally, a recent study by Staresina et al. (2009) showed that congruent events (a match of word/color combination during encoding, e.g., the word "balloon" in front of a yellow background) yielded greater activation in the left lateral inferior frontal gyrus than incongruent events (e.g., the word "elephant" in front of a red background). Activation in the lateral inferior frontal gyrus was stronger for later remembered than for forgotten trials, indicating that its involvement in the task is predictive of memory performance. Taken together, the inferior frontal gyrus may be critically involved in semantic processing of incoming information, which leads to better episodic memory.

Besides the left inferior frontal gyrus, the dorsolateral PFC is contributing to the effects of knowledge on memory as well, supposedly due to its role in building relationships between items (Murray and Ranganath, 2007). In Murray and Ranganath's (2007) study, participants saw sequentially presented unrelated word pairs and did either have to make a judgment concerning the relationship between the two words or concerning specific semantic attributes of the second word. Encoding the word pairs in relation to each other lead to a better recognition of the word pairs in an associative memory test. Activity in the dorsolateral PFC was greater in the relational judgment condition compared to the item-specific condition. Furthermore, activity in the dorsolateral PFC predicted performance in the associative memory test. These findings lead the authors to suggest that the dorsolateral PFC is involved in the active processing of semantic relationships (Murray and Ranganath, 2007).

In addition to semantic elaboration and relational processing, the lPFC is also heavily involved in memory control processes including monitoring. Memory control processes are crucial for evaluating representations retrieved from the HC in the context of current task goals, thereby allowing memory to be adaptive, in particular whenever the retrieved representations resemble each other or are both familiar (e.g., Ranganath et al., 2000; Mitchell and Johnson, 2009).

Taken together, findings on the involvement of the lPFC in memory processes related to knowledge use suggest that the lPFC is linked to intentional memorizing processes including semantic elaboration and relational processing. Given the literature

discussed above that suggests lPFC involvement in a number of memory processes related to knowledge use, we argue for the need to integrate the lPFC into the picture when dealing with the effects of prior knowledge on episodic memory. We will revisit this issue in the following sections.

CONCLUSIONS REGARDING NEUROIMAGING DATA

Recent neuroimaging findings suggest that both mPFC and MTL regions (particularly the HC) contribute to the formation and utilization of knowledge and that they do so in an interactive fashion. During the formation and application of complex conceptual knowledge, it is proposed that the mPFC and the HC interact in a way that the HC detects regularities across episodes, which are integrated with value information (such as gains and losses, as well as emotional valence) by the mPFC (Kumaran et al., 2009). Along similar lines, Nieuwenhuis and Takashima (2011) proposed that the mPFC integrates and weights information associated with discrete episodes from the limbic system, namely the HC, the amygdala, and the ventral striatum.

The neural correlates of memory processing in relation to prior knowledge also involve a network comprised of HC and mPFC. According to the model of van Kesteren et al. (2012), the HC is involved in the detection and encoding of novel information and information that is incongruent to the encoding context. The mPFC deals with relating and integrating the incoming information to the existing knowledge base. It acts like a resonance detector, in the sense that information congruent to prior knowledge resonates with existing information. HC and mPFC processes, however, do not work independently of one another. It is assumed that the HC encodes new experiences when novelty is high. When the mPFC detects resonance, it will inhibit (or compete with) the HC, as the new information can also be encoded via relation to prior knowledge. Therefore, examining the interactions between MTL and mPFC appears critical for understanding the effects of prior knowledge on memory. While the model has received initial support especially concerning the role of the mPFC in prior knowledge effects on memory, it has to be noted that the role of MTL regions in memory processing of congruent/incongruent information and its relation to mPFC is less clear and requires further consideration and validation.

In addition to the mPFC, we also discussed lPFC involvement in a number of memory processes related to knowledge use and argued for the need to integrate the lPFC into the picture when dealing with the effects of prior knowledge on memory. However, it is currently unclear how the medial and lateral parts of the PFC differ in their contribution to knowledge-related memory processes. The only explicit model available at the moment is one that focuses on neural correlates of the predictive function of memory that is based upon prior knowledge (Kroes and Fernández, 2012). In this framework, the mPFC is assumed to contribute to the formation of complex episodic memories and abstract knowledge, while the lateral PFC contributes to simple rule learning. Concisely, the lPFC is suggested to interact with the lateral/inferior temporal cortex and to apply strict stimulus-response rules, whereas the mPFC acts in concert with the HC to allow predictions based on abstract knowledge transferable to new situations. These postulations will need to be tested empirically.

Observing the involvements of mPFC and HC in both the formation of knowledge and in the use of knowledge for memory, it is now tempting to ask (a) to what extent the localizations of mPFC and HC observed in these processes are overlapping within the same person, and (b) how the mPFC-HC activations/interactions observed in the building up of knowledge are related to the subsequent use of this knowledge in service of memory. These questions call for a study to track the building up of knowledge and the use of knowledge for memory within the same participants.

From a developmental viewpoint, the differentiation between medial and lateral parts of the PFC in relation to knowledge-related memory processing is very important. As we shall discuss in the sections below, the development of the effects of prior knowledge on memory have mostly been linked to functional and structural changes in the lPFC. Given that some regions within the mPFC also display a more protracted maturation trajectory (Shaw et al., 2008), there are potentially important changes within the functioning of the mPFC which support the above mentioned development by using prior knowledge in service of memory functioning.

THE DEVELOPMENTAL COGNITIVE NEUROSCIENCE PERSPECTIVE

Knowledge accumulates in the course of life through experiences during which the individual perceives and internalizes patterns in his or her environment. As the growth of knowledge is especially striking in early life, taking a developmental cognitive neuroscience approach with a focus on child development offers the unique possibility of exploring the effects of an expanding knowledge base on memory (Baltes et al., 2006; Craik and Bialystok, 2006).

First, we will provide an overview of general theorizing about developmental changes in cognition across the lifespan. Second, we will focus on how memory development is shaped by lifespan changes on a neural and behavioral level. For the discussion of developmental changes in the neural correlates of memory with age, we will focus on both structural and functional development of PFC and MTL and link changes in these areas to age differences in the use of prior knowledge for memory. We will expand on this topic by highlighting parallel changes in the knowledge base, which speaks to the issue of differences in the use of prior knowledge with age. As we will show, these parallels are particularly salient during child development, as childhood is the most dynamic period of knowledge development (e.g., Li et al., 2004).

Hence, in the present review, the lifespan perspective provides the frame for conceptualizing the specifics concerning the influence of an emerging knowledge base on memory during childhood. We will argue that, to measure age differences in the effects of prior knowledge on episodic memory, it is necessary to distinguish the availability of prior knowledge from its accessibility.

GENERAL CONCEPTIONS OF LIFESPAN CHANGES IN COGNITION

Knowledge is known to increase strikingly during childhood, to continue to accumulate throughout adulthood, to remain rather stable in old age, and to only decrease in very old age (Baltes, 1987; Li et al., 2004; Craik and Bialystok, 2006). As emphasized by Craik and Bialystok (2006), however, knowledge does not act independently. Even if there is no decrease in available knowledge with age,

aging goes along with difficulties to access this knowledge. Older adults often express problems naming known objects even though, in principle, the names are available to them. This impairment in older adults could be linked to a temporary inability to access their knowledge, which can be overcome by giving appropriate cues or by offering more time (Cohen and Burke, 1993; Hasher et al., 2001). This nicely illustrates that knowledge can be available, but not accessible. In the framework offered by Craik and Bialystok (2006), the decrease in the ability to access knowledge is subsumed under the term cognitive control, which is known to increase steeply from infancy to young adulthood, and to decline thereafter (Bunge et al., 2002; Diamond, 2002; Zelazo et al., 2004).

The framework by Craik and Bialystok (2006) resembles the two-component model of lifespan cognition by Baltes et al. (2006). With regard to intellectual functioning across the lifespan, Baltes and colleagues distinguish between the mechanics and the pragmatics of cognition. The former are closely associated with the biological brain status, known to increase until early adulthood, and to decrease constantly thereafter. The latter are associated with the knowledge base, which is shaped by the socio-cultural environment. The cognitive pragmatics are shown to increase well into adulthood and to remain relatively stable until old age (Li et al., 2004). These comprehensive frameworks of cognitive change across the lifespan support the claim that the availability of knowledge on the one hand, and control processes allowing access to this knowledge on the other hand, follow strikingly different lifespan trajectories. Hence, when comparing age groups across the lifespan regarding a specific domain such as episodic memory, the common and unique contributions of cognitive mechanics and pragmatics need to be taken into account.

CONCEPTIONS OF LIFESPAN CHANGES IN EPISODIC MEMORY AND THE NEED TO INTEGRATE THE PRIOR KNOWLEDGE PERSPECTIVE

Grounded in the comprehensive treatments of lifespan cognitive development, Shing, Werkle-Bergner, Lindenberger and colleagues [Shing et al. (2008, 2010); Werkle-Bergner et al. (2006)] proposed a framework that distinguishes two components to account for changes in episodic memory across the lifespan: an associative component, which refers to mechanisms of binding different features of a memory episode into a coherent representation, and a strategic component referring to control processes which aid both encoding and retrieval. The two components are assumed to interact and to differ in terms of their lifespan trajectory. The associative component, which is linked to the development of the MTL, is proposed to reach its high functionality already in middle childhood. The strategic component, which is linked to the development of the PFC, is assumed to show a protracted development and to increase in its functionality until young adulthood. Both components are hypothesized to undergo senescent decline in late adulthood and old age. Therefore, children's difficulties in episodic memory performance are linked to immature strategic operations, whereas deficits among older adults are linked to impairments in both associative and strategic operations (Werkle-Bergner et al., 2006; Shing et al., 2008, 2010).

So far, there is no explicit handling of the general knowledge base's lifespan changes in relation to the associative and strategic components of memory development. Nevertheless, understanding lifespan changes of the general knowledge base may contribute to an improved understanding of memory development. Initial evidence for this view comes from research on expertise and memory performance. Schneider et al. (1993) compared children and adults with both high and low chess expertise. The children and adults with high expertise remembered chess positions comparably well and much better than children and adults with low expertise. In a control digit span task, adults outperformed children, independent of chess expertise. This lead the authors to conclude that a rich knowledge base of a specific domain strongly affects memory for newly learned information within that domain and can even lead to a reversal of typical age trends.

Relating these findings to the two-component framework of lifespan changes in episodic memory (Shing et al., 2008, 2010), one could argue that prior knowledge exerts its influence on the strategic component only, as controlling for strategic operations attenuates performance differences between children and young adults (Brehmer et al., 2007; Shing et al., 2008). Indeed, as discussed above, PFC-driven strategic encoding and retrieval operations such as elaborative encoding or explicit memory search play a role in the observed memory benefits (Craik and Tulving, 1975; Anderson, 1981), presumably via affecting the accessibility of prior knowledge. Recent findings from neuroimaging, however, revealed joint changes in mPFC and HC activation and in the connectivity between the two that underpin the emergence and application of prior knowledge (Kumaran et al., 2009, 2012; van Kesteren et al., 2010a,b). Furthermore, system-level consolidation was shown to be facilitated when relevant prior knowledge was available (Tse et al., 2007). These findings suggest that prior knowledge might do more than just influence PFC-driven strategic operations; they suggest that prior knowledge drives the interaction between PFC and MTL regions, possibly leading to more efficient learning and consolidation processes (van Kesteren et al., 2010a,b). These novel findings call for further theoretical specification and empirical validation of the two-component framework incorporating knowledge base as a possible factor driving the interaction between the strategic and the associative component.

DEVELOPMENT OF NEURAL CORRELATES OF MEMORY DURING CHILDHOOD

As discussed above, MTL and PFC regions are crucially related to (a) the formation and application of knowledge and (b) episodic memory functioning. As apparent from structural neuroimaging work on brain development, these regions exhibit differential developmental trajectories. While maturation takes longest in prefrontal and parietal areas, the MTL as a whole does not show large structural changes during early and middle childhood, even though this might be different for some subregions (Sowell et al., 2003; Gogtay et al., 2006; Lavenex and Lavenex, 2013). The mPFC seems to display a more complex maturation trajectory that differs between the subregions (Shaw et al., 2008). Concisely, the orbital and posterior parts (BA 25, BA 32, posterior parts of BA 12 and BA 11) of the mPFC follow an early maturation pattern, whereas its anterior and dorsal parts (BA 10 and anterior parts of BA 12 and BA 11) follow the trajectory of the lateral PFC, which is late maturing (Shaw et al., 2008).

These structural findings suggest that functions associated with the PFC (i.e., strategic/control processes) might develop more slowly than the ones associated with the MTL (i.e., associative processes). This idea is supported by a study in which the subsequent memory paradigm was used to reveal activations associated with successful remembering (Ofen et al., 2007). Ofen et al. (2007) showed that activation for later remembered scenes in contrast to forgotten scenes increases with age in the PFC, but not in the MTL (see converging behavioral findings from Brehmer et al., 2007; Shing et al., 2008).

There is, however, also evidence for continued functional development in MTL regions until early adolescence (Ghetti et al., 2010). In Ghetti et al.'s (2010) study, children (aged 8–11), adolescents (aged 14), and young adults were given an incidental encoding task in which they saw colored drawings and had to decide whether the depicted object could be found in a house or whether the object was animate. Later, in a surprise recognition task, participants were asked to state whether they had seen the drawing in the scanner and, if so, in what color. For this detail recollection task, adults and adolescents engaged regions of the HC and of the posterior parahippocampal gyrus, whereas children did not. This study differs from Ofen et al. (2007) as it entails a greater need for recollection processes due to the requirement of remembering contextual details of the encoding episode (the color of the drawing, which was randomly assigned). Therefore, age differences in MTL involvement in an episodic memory task might also be dependent on task factors such as the demand for associative binding. Whereas MTL regions can therefore be considered critical for the formation of new episodic memories, their role for the acquisition of knowledge is less clear. An early study by Vargha-Khadem et al. (1997) revealed that early hippocampal damage does not preclude the acquisition of new knowledge, as their patients, despite suffering from damage to the HC from early age on, showed average performance in tests of factual knowledge.

In addition to changes in MTL and PFC regions, age-related changes in brain areas specialized for specific domain knowledge may come along with age differences in memory as well (Ofen, 2012). Evidence can be gathered both from behavioral studies on the influence of growth in knowledge base on memory (reviewed in the next section), and from recent neuroimaging findings. These studies revealed prolonged maturation in brain areas processing specific domain knowledge and linked this maturation to increases in memory performance (Golarai et al., 2007; Chai et al., 2010). By comparing children, adolescents, and young adults, Golarai et al. (2007) showed that the right fusiform face area and the left parahippocampal place area, two functionally defined areas important for faces and places, showed a substantial age-related increase in size. Moreover, this increase was correlated with improved recognition memory for faces and places. In a similar vein, a subsequent study by Chai et al. (2010) showed that the age-related expansion of the parahippocampal place area is correlated with better memory for complex scenes in participants aged 8–24.

In sum, brain regions that underpin memory differ regarding the time course during which they develop. While MTL regions are relatively mature already during middle childhood (but see Ghetti et al., 2010), the lPFC and parts of the mPFC show a protracted development which continues until late adolescence/young adulthood. Taking into account brain areas that are specialized for specific domain knowledge adds to this pattern as those areas display a prolonged maturation that could be related to memory performance. While the distinction between influences of PFC- and MTL-development on memory performance has recently gained considerable attention (see e.g., Ofen et al., 2007; Ghetti et al., 2010; Shing et al., 2010), future research will have to take the development of domain-specific areas into account as well.

DEVELOPMENT OF KNOWLEDGE AND ITS RELATION TO THE NEURAL CORRELATES OF MEMORY

As discussed thus far, more elaborated semantic networks contribute to memory improvements with age. In accordance with this, children's episodic memory has been shown to be influenced by their semantic knowledge about the to-be-remembered stimuli. For example, in an early study by Schneider et al. (1989), children (third, fifth, and seventh graders) who possessed a broad knowledge of soccer showed better recall of a soccer story than children that did not possess such soccer-related knowledge.

Earlier behavioral studies that assessed congruency effects in children of different ages revealed an age-related increase in the tendency to remember congruent information as opposed to incongruent information (Geis and Hall, 1978; Ghatala et al., 1980, for a meta-analysis see Stangor and McMillan, 1992). For example, in Ghatala et al. (1980), children aged 8–14 answered questions about 36 words that were either congruent with the questions (yes-answers) or incongruent (no-answers) and had to recall the words afterwards. A linear increase in recall accuracy with age was found for the congruent condition, whereas no change in recall accuracy with age was found for the incongruent condition. This increase in congruency effect with age was interpreted based on the levels-of-processing framework (Craik and Lockhart, 1972): although all words can be understood by all participants, older children have more opportunities to elaborate on the to-be encoded word because semantic knowledge grows with age. Ghatala et al. (1980), however, acknowledge that their findings are also consistent with a retrieval-related interpretation. This interpretation would suggest that older children engage more in strategic retrieval and might use the encoding questions as cues during recall, which is easier if the word matches its question (i.e., is congruent).

In a study with children aged 8–11, Maril et al. (2011) used the semantic congruency effect to manipulate the accessibility of prior knowledge in an item-color pairing paradigm, in which subjects had to decide whether a word/color combination was plausible. In an fMRI-analysis which took into account congruency as well as age, Maril et al. (2011) showed that adults rely more on structures in the parietal cortex and in the left lPFC (which, as mentioned before, can be linked to semantic processing), whereas children recruit more posterior brain areas (i.e., the right occipital cortex) associated with perceptual processing. Based on these findings, Maril et al. (2011) suggest that children may initially depend more on posterior perceptual systems in service of memory functioning, and, with age, develop more elaborative (semantic) knowledge structures. This extensive semantic knowledge base is then used for a more elaborative encoding, which, as shown by a main effect of age, is generally beneficial for memory.

In sum, Maril et al.'s (2011) study on the neural correlates of an age-related increase in the congruency effect suggests a rise in the use of semantic knowledge structures for remembering (Maril et al., 2011). This might go along with a decreasing importance of mere perceptual encoding, as indicated by a posterior-to-anterior shift in brain activation, and with an increasing importance of PFC-driven strategic encoding. This reasoning is in accordance with the developmental trajectory of gist vs. verbatim knowledge as proposed by Brainerd et al. (2004), a notion that we will turn to in the next section. Thus far, however, most developmental studies have not disentangled age-related differences between the availability and the accessibility and use of prior knowledge. We will discuss these issues in the summary section.

THE FLIPSIDE OF KNOWLEDGE DEVELOPMENT

Does the accumulation of knowledge in the course of life improve memory performance in all situations? Evidence against this view is provided by research on false memory. In the DRM-paradigm (Deese, 1959; Roediger and McDermott, 1995), words that semantically converge to a common theme are presented during encoding. Later at recognition, participants are tested on their memory for the words studied beforehand. In addition, semantically related words never studied at encoding (*critical lures*) are also presented and participants are asked to reject those lures. In adult participants, the probability of falsely endorsing the critical lures is as high as that of the presented items. False recognition of semantically related words increases during childhood (Metzger et al., 2008; Paz-Alonso et al., 2008). Using the DRM-paradigm, Paz-Alonso et al. (2008) showed a correlation between the age-related increase in false alarms to critical lures and activation changes in the left ventrolateral PFC, which has been shown to be important for semantic elaboration (Wagner et al., 1998).

The DRM-paradigm illustrates that the more elaborate semantic knowledge structures of older children may improve the extraction of gist-like traces as opposed to the less semantic processing of younger children. This in turn leads to a higher likelihood of endorsing critical lures in older children (for a similar argument, see Smith and Hunt, 1998). Similar findings could also be revealed in an induction task (Sloutsky and Fisher, 2004) in which category (semantically)-based induction and similarity (perceptually)-based induction were disentangled. Adults typically perform induction in a category-based (semantic) manner, whereas children rely more on similarity-based (perceptual) induction. Category-based induction led to little discrimination between items presented during the induction task and lures that belonged to the same semantic category (e.g., another exemplar of the category cat). Similar to the findings using the DRM-paradigm, children displayed a higher memory accuracy compared to adults, which was due to a lower false alarm rate. Accordingly, training children to perform category-based induction lead to a memory performance comparable to the one of adults (Sloutsky and Fisher, 2004). These results show that relying on prior knowledge is not always beneficial for episodic memory performance. In specific situations where perceptual information is important, a reversal of typical age effects, i.e., children outperforming adults, can be found. This is due to the children's stronger reliance on perceptual as compared to semantic processing, which is more prone to false memories because of overgeneralization.

SUMMARY AND OPEN QUESTIONS

In this review, we discussed the influence of prior knowledge on memory considering both the psychology and the cognitive neuroscience literature. We reviewed classical psychology experiments that demonstrate the impact of prior knowledge on remembering new information (Bransford and Johnson, 1972; Craik and Tulving, 1975). We integrated the emerging cognitive neuroscience perspective on this topic, which points to PFC and MTL regions displaying activity changes as a function of prior knowledge. More specifically, recent studies suggest a prominent role of the vmPFC and the HC in underpinning the formation and application of prior knowledge (Kumaran et al., 2009, 2012; van Kesteren et al., 2010a,b). Both areas were shown to play a key role in consolidation as well. This is a conceivable idea given that the effect of consolidation and the effect of knowledge formation and application resemble each other, i.e., forming of a conceptual "gist" which might later be applied as a search frame during retrieval. Moreover, recent research indicates an activity increase in the vmPFC during post-consolidation periods (e.g., Takashima et al., 2006), which may occur earlier if new information can be assimilated into existing knowledge structures (Tse et al., 2007).

In addition, we outlined a developmental cognitive neuroscience perspective, considering changes in brain structure and function across child development and linking those changes to behavioral research on age differences in the influence of prior knowledge on memory. To conclude, we will now outline open questions and possible confounds regarding the assessment and interpretation of age-related changes in the use of prior knowledge for remembering.

First, to assess age differential effects of prior knowledge on episodic memory in an age comparative setting, we postulate that it is necessary to distinguish the availability of prior knowledge from its accessibility and use. As mentioned above, one of the most prominent changes in human ontogeny is growth in knowledge, that is, an increase in the availability of prior knowledge. During the course of the review, we have discussed a number of studies (Ghatala et al., 1980; Schneider et al., 1989, 1993; Maril et al., 2011) which revealed that a certain amount of performance differences in memory tasks between children and adults can be attributed to adults knowing more about the to-be-remembered information. This was most prominently shown in experiments that compared children and adults, with the children being experts in a domain, whereas the adults are not. In this case, children can outperform adults in a memory task that is closely related to their field of expertise (e.g., Schneider et al., 1993). However, using expert groups of different age to uncover differential memory effects of availability vs. accessibility of prior knowledge comes along with difficulties as well, as there are many uncontrollable sources of differences between the age groups (for example, different histories of gaining expertise; Schneider et al., 1993). An alternative approach for future experiments might be to control the availability of prior knowledge either by carefully assessing the participants' knowledge of the stimulus material, or, perhaps even better, by experimentally inducing new knowledge structures that are comparable between

the different age groups. This experimentally induced knowledge subsequently serves as prior knowledge for the learning of new, related information. An example of this approach was provided in a recent behavioral study (Kumaran, 2013) in which it was shown that prior knowledge about a hierarchy facilitates transitive inference in a new, partly overlapping hierarchy. Participants first acquired a seven-item hierarchy and then performed transitive inference on two new nine-item hierarchies. One of the new nine-item hierarchies contained five items of the old seven-item hierarchy, arranged in their original position in the hierarchy (thus forming a scaffold), the other one was entirely new. Participants performed significantly better in the overlapping hierarchy condition as compared to the entirely new hierarchy. These results suggest that prior knowledge benefits transitive inference performance via a contextual transfer that relates new information to the existing knowledge scaffold.

In sum, studies that use experimentally induced knowledge can greatly benefit our understanding of the effects of prior knowledge on memory, especially for developmental questions They have several advantages: first, they allow careful monitoring of the knowledge available to the participant, thus excluding the possibility that knowledge structures are just not comparable between the two groups. Second, the degree of prior knowledge can be experimentally manipulated, which enables researchers to look at the effects of strength of prior knowledge on memory. Third, the phase during which the participants acquire the knowledge can itself be subject to investigation, which would allow relating learning performance to later memory performance. This would provide a link between work on the emergence of knowledge (e.g., Kumaran et al., 2009, 2012) with work on the effects of prior knowledge on memory (e.g., van Kesteren et al., 2010a,b).

Regarding the ability to access and use one's prior knowledge for memory, the PFC (both medial and lateral aspects) has been shown to be important. Recent studies on the use of prior knowledge for memory (van Kesteren et al., 2010a,b) point to a key role of the mPFC, which is assumed to act as a resonance detector to determine congruency with prior knowledge. When congruent information is detected, the mPFC might inhibit hippocampal activity and the information is directly integrated into existing knowledge structures (van Kesteren et al., 2012). This reasoning is in line with other claims suggesting that the mPFC provides a "feeling of rightness" during retrieval (Moscovitch and Winocur, 2002) and that it acts as a value integrator during the building up of knowledge (Kumaran et al., 2009). In an attempt to integrate these three conceptualizations, we hypothesize that the mPFC plays a monitoring role for episodic memories by providing an evaluation of fit of both internally and externally generated representations with prior knowledge. In line with a recent review (Nieuwenhuis and Takashima, 2011), we suggest that, based on this evaluation of fit, the mPFC impacts memory processing in the limbic system, especially in the HC.

Besides the mPFC, the lPFC is also important for memory processes related to accessing and using knowledge, including semantic elaboration and strategic encoding and retrieval (e.g., Wagner et al., 1998; Fletcher et al., 2000; Murray and Ranganath, 2007). These functions differ from the ones associated with the mPFC, which might indicate that mPFC and lPFC differ in their contribution to the effects of prior knowledge on memory, depending on the requirements of the memory task at hand. On the one hand, the mPFC might mainly be involved in situations that highlight the congruency of new information with prior knowledge, its task being to evaluate the fit between the target information and expectancies based on prior knowledge. This evaluation is particularly relevant when different behavioral choices are involved in the process of building up the prior knowledge (e.g., choices that entail gains or losses). On the other hand, the lPFC might be involved when there is a strategic/intentional attempt to integrate and relate new knowledge with existing knowledge structures. These conjectures will need to be validated empirically.

Coming back to the development of the use of prior knowledge for memory, the PFC, and in particular its lateral parts, is known to mature late and to reach its full functionality in early adulthood only (Sowell et al., 2003). Therefore, it seems plausible that children do not use their prior knowledge as efficiently as young adults do. This would point to a key role of the PFC in the development of the use of prior knowledge for memory and would also converge with general assumptions about the increasing influence of memory functions that are mediated by the PFC (Shing et al., 2010). Further evidence for this claim has been revealed in behavioral studies that point to an increase in the use of supposedly PFC-driven memory strategies well into adolescence (Schneider et al., 2002; Brehmer et al., 2007; Paz-Alonso et al., 2008; Shing et al., 2008). Accordingly, fMRI and event-related potential (ERP) studies could link the development of memory for context and details, known to particularly require strategic/cognitive control functions, to the maturation of PFC networks (e.g., Cycowicz et al., 2001; Ofen et al., 2007). Taken together, the literature on memory development so far has placed much emphasis on the lateral PFC as a driving force of age-related improvements in memory functioning across childhood.

In addition, we postulate that it is worthwhile taking a closer look on the developmental role that the mPFC may play in supporting knowledge use in memory. It is interesting to note that parts of the mPFC (Shaw et al., 2008) display a protracted structural development. The extent to which this has implications for the functional contributions of the mPFC to the access and use of prior knowledge for memory is yet unknown. If the functional developmental trajectory of parts of the mPFC relevant for knowledge processing resembles the trajectory of the lPFC, an increase in mPFC activation should track the increasing use of knowledge for memory with age. At the same time, due to the fact that children constantly have to build-up new knowledge and update their knowledge structures, the amount of available knowledge increases rapidly during childhood and adolescence. In Piagetian terms, accommodation (changing existing schemas) occurs as long as we continue to learn (Piaget, 1951). Therefore, the involvement of mPFC in building up knowledge may be starting early. Children, although being experts at building up new knowledge, seem to differ from young adults, however, when it comes to accessing and using knowledge strategically. Tackling the factors that limit the strategical use of knowledge by experimentally ensuring the existence of comparable knowledge structures in children and young adults will be highly interesting and relevant to developmental as well as educational scholars. Research into age differences in the use of prior knowledge for

memory might prospectively serve to foster learning environments that are better tailored to the way that children acquire knowledge. Given the working hypothesis that children do not use their knowledge as efficiently as young adults, it is tempting to search for ways to foster the use of knowledge in children, for example via training the children on memory strategies (e.g., Brehmer et al., 2007; Shing et al., 2008). An efficient use of knowledge may eliminate age differences in learning and memory performance, as shown in the expertise literature (e.g., Schneider et al., 1993).

In sum, our knowledge of the world is quickly changing and increasing during the first decades of the lifespan. Therefore, a developmental perspective on understanding how the human brain makes use of its accumulated knowledge and how it guides future learning as well as behavior, seems to be highly called for.

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REFERENCES

Addis, D. R., and McAndrews, M. P. (2006). Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding. *Neuroimage* 33, 1194–1206. doi:10.1016/j.neuroimage.2006.07.039

Alba, J. W., and Hasher, L. (1983). Is memory schematic? *Psychol. Bull.* 93, 203. doi:10.1037/0033-2909.93.2.203

Andersen, P., Morris, R. G. M., Amaral, D., Bliss, T., and O'Keefe, J. (eds) (2007). *The Hippocampus Book*. New York: Oxford University Press.

Anderson, J. R. (1981). Effects of prior knowledge on memory for new information. *Mem. Cognit.* 9, 237–246.

Baltes, P. B. (1987). Theoretical propositions of life-span developmental psychology: on the dynamics between growth and decline. *Dev. Psychol.* 23, 611–626. doi:10.1037/0012-1649.23.5.611

Baltes, P. B., Lindenberger, U., and Staudinger, U. M. (2006). "Life-span theory in developmental psychology," in *Handbook of Child Psychology: Vol. 1. Theoretical Models of Human Development*, Series edited by W. Damon and Vol. edited by R. M. Lerner, 6th ed., (New Jersey: Wiley), 569–664.

Bartlett, F. C. (1932). *Remembering: A Study in Experimental and Social Psychology*. Cambridge: Cambridge University Press.

Behrens, T. E. J., Hunt, L. T., Woolrich, M. W., and Rushworth, M. F. S. (2008). Associative learning of social value. *Nature* 456, 245–249. doi:10.1038/nature07538

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci.* 15, 527–536. doi:10.1016/j.tics.2011.10.001

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex.* 19, 2767–2796. doi:10.1093/cercor/bhp055

Brainerd, C. J., Holliday, R. E., and Reyna, V. F. (2004). Behavioral measurement of remembering phenomenologies: so simple a child can do it. *Child Dev.* 75, 505–522. doi:10.1111/j.1467-8624.2004.00689.x

Bransford, J. D., and Johnson, M. K. (1972). Contextual prerequisites for understanding: some investigations of comprehension and recall. *J. Verbal Learn. Verbal Behav.* 11, 717–726. doi:10.1016/S0022-5371(72)80006-9

Brehmer, Y., Li, S.-C., Müller, V., von Oertzen, T., and Lindenberger, U. (2007). Memory plasticity across the life span: uncovering children's latent potential. *Dev. Psychol.* 43, 465–478. doi:10.1037/0012-1649.43.2.465

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., and Gabrieli, J. D. E. (2002). Immature frontal lobe contributions to cognitive control in children. *Neuron* 33, 301–311. doi:10.1016/S0896-6273(01)00583-9

Chai, X. J., Ofen, N., Jacobs, L. F., and Gabrieli, J. D. E. (2010). Scene complexity: influence on perception, memory, and development in the medial temporal lobe. *Front. Hum. Neurosci.* 4, doi:10.3389/fnhum.2010.00021

Cohen, G., and Burke, D. M. (1993). Memory for proper names: a review. *Memory* 1, 249–263. doi:10.1080/09658219308258237

Craik, F. I. M., and Bialystok, E. (2006). Cognition through the lifespan: mechanisms of change. *Trends Cogn. Sci.* 10, 131–138. doi:10.1016/j.tics.2006.01.007

Craik, F. I. M., and Lockhart, R. S. (1972). Levels of processing: a framework for memory research. *J. Verbal Learn. Verbal Behav.* 11, 671–684. doi:10.1016/S0022-5371(72)80001-X

Craik, F. I. M., and Tulving, E. (1975). Depth of processing and the retention of words in episodic memory. *J. Exp. Psychol. Gen.* 104, 268–294. doi:10.1037/0096-3445.104.3.268

Cycowicz, Y. M., Friedman, D., Snodgrass, J. G., and Duff, M. (2001). Recognition and source memory for pictures in children and adults. *Neuropsychologia* 39, 255–267. doi:10.1016/S0028-3932(00)00108-1

Deese, J. (1959). On the prediction of occurrence of particular verbal intrusions in immediate recall. *J. Exp. Psychol.* 58, 17–22. doi:10.1037/h0046671

Diamond, A. (2002). "Normal development of prefrontal cortex from birth to young adulthood: cognitive functions, anatomy, and biochemistry," in *Principles of Frontal Lobe Function*, eds D. T. Stuss and R. T. Knight (New York: Oxford University Press), 466–503.

Duncan, K., Curtis, C., and Davachi, L. (2009). Distinct memory signatures in the hippocampus: intentional states distinguish match and mismatch enhancement signals. *J. Neurosci.* 29, 131–139. doi:10.1523/JNEUROSCI.2998-08.2009

Dunlosky, J., Hunt, R. R., and Clark, E. (2000). Is perceptual salience needed in explanations of the isolation effect? *J. Exp. Psychol. Learn. Mem. Cogn.* 26, 649–657. doi:10.1037/0278-7393.26.3.649

Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D., and Walker, M. P. (2007). Human relational memory requires time and sleep. *Proc. Natl. Acad. Sci. U.S.A.* 104, 7723–7728. doi:10.1073/pnas.0700094104

Fletcher, P. C., Shallice, T., and Dolan, R. (2000). Sculpting the response space – an account of left prefrontal activation at encoding. *Neuroimage* 12, 404–417. doi:10.1006/nimg.2000.0633

Frankland, P. W., and Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130. doi:10.1038/nrn1607

Gais, S., Albouy, G., Boly, M., Dang-Vu, T. T., Darsaud, A., Desseilles, M., et al. (2007). Sleep transforms the cerebral trace of declarative memories. *Proc. Natl. Acad. Sci. U.S.A.* 104, 18778–18783. doi:10.1073/pnas.0705454104

Geis, M. F., and Hall, D. M. (1978). Encoding and congruity in children's incidental memory. *Child Dev.* 49, 857–861. doi:10.2307/1128256

Ghatala, E. S., Carbonari, J. P., and Bobele, L. Z. (1980). Developmental changes in incidental memory as a function of processing level, congruity, and repetition. *J. Exp. Child Psychol.* 29, 74–87. doi:10.1016/0022-0965(80)90092-2

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., and Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *J. Neurosci.* 30, 9548–9556. doi:10.1523/JNEUROSCI.3500-09.2010

Gilboa, A., Alain, C., Stuss, D. T., Melo, B., Miller, S., and Moscovitch, M. (2006). Mechanisms of spontaneous confabulations: a strategic retrieval account. *Brain* 129, 1399–1414. doi:10.1093/brain/awl093

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., et al. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus* 16, 664–672. doi:10.1002/hipo.20193

Golarai, G., Ghahremani, D. G., Whitfield-Gabrieli, S., Reiss, A., Eberhardt, J. L., Gabrieli, J. D. E., et al. (2007). Differential development of high-level visual cortex correlates with category-specific recognition memory. *Nat. Neurosci.* 10, 512–522.

Hasher, L., Tonev, S. T., Lustig, C., and Zacks, R. T. (2001). "Inhibitory control, environmental support, and self-initiated processing in aging," in *Perspectives on Human Memory and Cognitive Aging: Essays in Honour of Fergus Craik*, eds M. Naveh-Benjamin, M. Moscovitch, and H. L. Roediger (New York: Psychology Press), 286–297.

Hunt, R. R., and Lamb, C. A. (2001). What causes the isolation effect? *J. Exp. Psychol. Learn. Mem. Cogn.* 27, 1359–1366. doi:10.1037/0278-7393.27.6.1359

Kapur, S., Craik, F. I., Tulving, E., Wilson, A. A., Houle, S., and Brown, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. *Proc. Natl. Acad. Sci. U.S.A.* 91, 2008–2011. doi: 10.1073/pnas.91.6.2008

Köhler, W., and von Restorff, H. (1937). Analyse von Vorgängen im Spurenfeld. *Psychol. Forsch.* 21, 56–112. doi: 10.1007/BF02441202

Kroes, M. C. W., and Fernández, G. (2012). Dynamic neural systems enable adaptive, flexible memories. *Neurosci. Biobehav. Rev.* 36, 1646–1666. doi:10.1016/j.neubiorev.2012.02.014

Kumaran, D. (2013). Schema-driven facilitation of new hierarchy learning in the transitive inference paradigm. *Learn. Mem.* 20, 388–394. doi:10.1101/lm.030296.113

Kumaran, D., and McClelland, J. L. (2012). Generalization through the recurrent interaction of episodic memories: a model of the hippocampal system. *Psychol. Rev.* 119, 573–616. doi:10.1037/a0028681

Kumaran, D., Melo, H. L., and Duzel, E. (2012). The emergence and representation of knowledge about social and nonsocial hierarchies. *Neuron* 76, 653–666. doi:10.1016/j.neuron.2012.09.035

Kumaran, D., Summerfield, J. J., Hassabis, D., and Maguire, E. A. (2009). Tracking the emergence of conceptual knowledge during human decision making. *Neuron* 63, 889–901. doi:10.1016/j.neuron.2009.07.030

Lavenex, P., and Lavenex, P. B. (2013). Building hippocampal circuits to learn and remember: insights into the development of human memory. *Behav. Brain Res.* 254, 8–21. doi:10.1016/j.bbr.2013.02.007

Li, S.-C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W., and Baltes, P. B. (2004). Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. *Psychol. Sci.* 15, 155–163. doi:10.1111/j.0956-7976.2004.01503003.x

Maguire, E. A., Frith, C. D., and Morris, R. G. M. (1999). The functional neuroanatomy of comprehension and memory: the importance of prior knowledge. *Brain* 122, 1839–1850. doi:10.1093/brain/122.10.1839

Maril, A., Avital, R., Reggev, N., Zuckerman, M., Sadeh, T., Ben Sira, L., et al. (2011). Event congruency and episodic encoding: a developmental fMRI study. *Neuropsychologia* 49, 3036–3045. doi:10.1016/j.neuropsychologia.2011.07.004

Marr, D. (1971). Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 262, 23–81. doi:10.1098/rstb.1971.0078

McClelland, J. L., McNaughton, B. L., and O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457. doi:10.1037/0033-295X.102.3.419

McKenzie, S., Robinson, N. T. M., Herrera, L., Churchill, J. C., and Eichenbaum, H. (2013). Learning causes reorganization of neuronal firing patterns to represent related experiences within a hippocampal schema. *J. Neurosci.* 33, 10243–10256. doi:10.1523/JNEUROSCI.0879-13.2013

Metzger, R. L., Warren, A. R., Shelton, J. T., Price, J., Reed, A. W., and Williams, D. (2008). Do children "DRM" like adults? False memory production in children. *Dev. Psychol.* 44, 169–181. doi:10.1037/0012-1649.44.1.169

Mitchell, K. J., and Johnson, M. K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory? *Psychol. Bull.* 135, 638–677. doi:10.1037/a0015849

Moscovitch, M., and Craik, F. I. M. (1976). Depth of processing, retrieval cues, and uniqueness of encoding as factors in recall. *J. Verbal Learn. Verbal Behav.* 15, 447–458.

Moscovitch, M., and Winocur, G. (2002). "The frontal cortex and working with memory," in *Principles of Frontal Lobe Function*, eds D. T. Stuss and R. T. Knight (New York: Oxford University Press), 188–209.

Murray, L. J., and Ranganath, C. (2007). The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *J. Neurosci.* 27, 5515–5522. doi:10.1523/JNEUROSCI.0406-07.2007

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* 7, 217–227. doi:10.1016/S0959-4388(97)80010-4

Nieuwenhuis, I. L. C., and Takashima, A. (2011). The role of the ventromedial prefrontal cortex in memory consolidation. *Behav. Brain Res.* 218, 325–334. doi:10.1016/j.bbr.2010.12.009

Northoff, G., and Bermpohl, F. (2004). Cortical midline structures and the self. *Trends Cogn. Sci.* 8, 102–107. doi:10.1016/j.tics.2004.01.004

Ofen, N. (2012). The development of neural correlates for memory formation. *Neurosci. Biobehav. Rev.* 36, 1708–1717.

Ofen, N., Kao, Y.-C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2007). Development of the declarative memory system in the human brain. *Nat. Neurosci.* 10, 1198–1205. doi:10.1038/nn1950

Paz-Alonso, P. M., Ghetti, S., Donohue, S. E., Goodman, G. S., and Bunge, S. A. (2008). Neurodevelopmental correlates of true and false recognition. *Cereb. Cortex* 18, 2208–2216. doi:10.1093/cercor/bhm246

Piaget, J. (1929). *The Child's Conception of the World*, trans. J. Tomlinson, and A. Thomlinson, (New York: Harcourt Brace).

Piaget, J. (1951). *Play, Dreams and Imitation in Childhood.* London: Routledge.

Ranganath, C., Johnson, M. K., and D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J. Neurosci.* 20, RC108.

Reber, P. J., Siwiec, R. M., Gitelman, D. R., Parrish, T. B., Mesulam, M. M., and Paller, K. A. (2002). Neural correlates of successful encoding identified using functional magnetic resonance imaging. *J. Neurosci.* 22, 9541–9548.

Roediger, H. L., and McDermott, K. B. (1995). Creating false memories: remembering words not presented in lists. *J. Exp. Psychol. Learn. Mem. Cogn.* 21, 803–814. doi:10.1037/0278-7393.21.4.803

Rojahn, K., and Pettigrew, T. F. (1992). Memory for schema-relevant information: a meta-analytic resolution. *Br. J. Soc. Psychol.* 31, 81–109. doi:10.1111/j.2044-8309.1992.tb00958.x

Schneider, W., Gruber, H., Gold, A., and Opwis, K. (1993). Chess expertise and memory for chess positions in children and adults. *J. Exp. Child Psychol.* 56, 328–349. doi:10.1006/jecp.1993.1038

Schneider, W., Knopf, M., and Stefanek, J. (2002). The development of verbal memory in childhood and adolescence: findings from the Munich longitudinal study. *J. Educ. Psychol.* 94, 751–761. doi:10.1037/0022-0663.94.4.751

Schneider, W., Körkel, J., and Weinert, F. E. (1989). Domain-specific knowledge and memory performance: a comparison of high- and low-aptitude children. *J. Educ. Psychol.* 81, 306–312. doi:10.1037/0022-0663.81.3.306

Schulman, A. I. (1974). Memory for words recently classified. *Mem. Cognit.* 2, 47–52.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., et al. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *J. Neurosci.* 28, 3586–3594. doi: 10.1523/JNEUROSCI.5309-07.2008

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S.-C., and Lindenberger, U. (2010). Episodic memory across the lifespan: the contributions of associative and strategic components. *Neurosci. Biobehav. Rev.* 34, 1080–1091.

Shing, Y. L., Werkle-Bergner, M., Li, S.-C., and Lindenberger, U. (2008). Associative and strategic components of episodic memory: a lifespan dissociation. *J. Exp. Psychol. Gen.* 137, 495–513. doi:10.1037/0096-3445.137.3.495

Simons, J. S., and Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nat. Rev. Neurosci.* 4, 637–648. doi: 10.1038/nrn1178

Sloutsky, V. M., and Fisher, A. V. (2004). When development and learning decrease memory: evidence against category-based induction in children. *Psychol. Sci.* 15, 553–558. doi: 10.1111/j.0956-7976.2004.00718.x

Smith, R. E., and Hunt, R. R. (1998). Presentation modality affects false memory. *Psychon. Bull. Rev.* 5, 710–715. doi:10.1037/a0022217

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., and Toga, A. W. (2003). Mapping cortical change across the human life span. *Nat. Neurosci.* 6, 309–315. doi:10.1038/nn1008

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231. doi:10.1037/0033-295X.99.3.582

Stangor, C., and McMillan, D. (1992). Memory for expectancy-congruent and expectancy-incongruent information: a review of the social and social developmental literatures. *Psychol. Bull.* 111, 42–61. doi:10.1037/0033-2909.111.1.42

Staresina, B. P., Gray, J. C., and Davachi, L. (2009). Event congruency enhances episodic memory encoding through semantic elaboration and relational binding. *Cereb. Cortex* 19, 1198–1207. doi:10.1093/cercor/bhn165

Takashima, A., Nieuwenhuis, I. L. C., Jensen, O., Talamini, L. M., Rijpkema, M., and Fernandez, G. (2009). Shift from hippocampal to

neocortical centered retrieval network with consolidation. *J. Neurosci.* 29, 10087–10093. doi:10.1523/JNEUROSCI.0799-09.2009

Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M. J., et al. (2006). Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proc. Natl. Acad. Sci. U.S.A.* 103, 756–761. doi:10.1073/pnas.0507774103

Treves, A., and Rolls, E. T. (1992). Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus* 2, 189–199. doi:10.1002/hipo.450020209

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., et al. (2007). Schemas and memory consolidation. *Science* 316, 76–82. doi:10.1126/science.1135935

Tse, D., Takeuchi, T., Kakeyama, M., Kajii, Y., Okuno, H., Tohyama, C., et al. (2011). Schema-dependent gene activation and memory encoding in neocortex. *Science* 333, 891–895. doi:10.1126/science.1205274

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–402.

van Kesteren, M. T. R., Beul, S. F., Takashima, A., Henson, R. N., Ruiter, D. J., and Fernández, G. (2013). Differential roles for medial prefrontal cortex and medial temporal cortices in schema-dependent encoding: from congruent to incongruent. *Neuropsychologia.* doi:10.1016/j.neuropsychologia.2013.05.027

van Kesteren, M. T. R., Fernández, G., Norris, D. G., and Hermans, E. J. (2010a). Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. *Proc. Natl. Acad. Sci. U.S.A.* 107, 7550–7555. doi:10.1073/pnas.0914892107

van Kesteren, M. T. R., Rijpkema, M., Ruiter, D. J., and Fernández, G. (2010b). Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity. *J. Neurosci.* 30, 15888–15894. doi:10.1523/JNEUROSCI.2674-10.2010

van Kesteren, M. T. R., Ruiter, D. J., Fernández, G., and Henson, R. N. (2012). How schema and novelty augment memory formation. *Trends Neurosci.* 35, 211–219. doi:10.1016/j.tins.2012.02.001

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277, 376–380. doi:10.1126/science.277.5324.376

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., et al. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 281, 1188–1191. doi:10.1126/science.281.5380.1188

Wang, S.-H., and Morris, R. G. M. (2010). Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. *Annu. Rev. Psychol.* 61, 49–79. doi:10.1146/annurev.psych.093008.100523

Werkle-Bergner, M., Müller, V., Li, S.-C., and Lindenberger, U. (2006). Cortical EEG correlates of successful memory encoding: implications for lifespan comparisons. *Neurosci. Behav. Rev.* 30, 839–854.

Yamashita, K. I., Hirose, S., Kunimatsu, A., Aoki, S., Chikazoe, J., Jimura, K., et al. (2009). Formation of long-term memory representation in human temporal cortex related to pictorial paired associates. *J. Neurosci.* 29, 10335–10340. doi:10.1523/JNEUROSCI.1328-09.2009

Yassa, M. A., and Stark, C. (2011). Pattern separation in the hippocampus. *Trends Neurosci.* 34, 515–525. doi:10.1016/j.tins.2011.06.006

Zeithamova, D., and Preston, A. R. (2010). Flexible memories: differential roles for medial temporal lobe and prefrontal cortex in cross-episode binding. *J. Neurosci.* 30, 14676–14684. doi:10.1523/JNEUROSCI.3250-10.2010

Zelazo, P. D., Craik, F. I. M., and Booth, L. (2004). Executive function across the life span. *Acta Psychol.* 115, 167–183. doi:10.1016/j.actpsy.2003.12.005

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Developmental trajectories of associative memory from childhood to adulthood: a behavioral and neuroimaging study

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Episodic memory refers to the capacity to bind multimodal memories to constitute a unique personal event. Most developmental studies on episodic memory focused on one specific component, i.e., the core factual information. The present study examines the relevance of a novel episodic paradigm to assess its developmental trajectories in a more comprehensive way according to the type of association (item-feature, item-location, and item-sequence associations) with measures of both objective and subjective recollection. We conducted a behavioral study aimed at testing the effects of age in a large sample of 160 children, adolescents, and young adults (6–23 years old). We confronted the behavioral data to the neural correlates in a subgroup of 30 children using voxel-based morphometry. Behavioral data outlined differential developmental trajectories according to the type of association, with a continuous increase of factual associative memory efficiency until 10 years, a linear increase of performance in spatial associative memory that pursues until early adulthood and an abrupt increase in temporal associative memory efficiency between 9 and 10. Regarding recollection, measures showed a more pronounced enhancement from 9 to 10 years. Hence, behavioral data highlight a peculiar period in late childhood (8–10 years old) crucial for the developmental time course of episodic memory. Regarding structural data, we found that the improvement of associative memory efficiency was related to a decrease in gray matter volume in a large cerebral network including the dorsolateral and ventrolateral prefrontal cortex (and superior and anterior temporal regions), and the hippocampus bilaterally. These data suggest that multimodal integration would probably be related to the maturation of temporal regions and modulated by a fronto-parietal network. Besides, our findings emphasize the relevance of the present paradigm to assess episodic memory especially in the clinical setting.

Keywords: episodic memory, associative memory, spatial memory, sequential memory, recollection, structural imaging

INTRODUCTION

Episodic memory refers to the most complex human memory system that emerges in early childhood. It requires both the individual's self-awareness (i.e., autonoetic) of having personally experienced a past event while retrieving the overall phenomenological details (i.e., context or source) bound to that unique moment (which gives a peculiar vividness to the recall) and the ability to make sense of this recall for future experiences (Tulving, 2002). Thus, episodic memory processes rely on the binding of different types of associations, i.e., both within-domain associations such as inter-item associations (e.g., child and flower) and between-domain associations such as item-location associations (e.g., child and behind-window) (Mayes et al., 2007). These associations may be integrated into a single representation (e.g., the child standing behind the window) and may elicit a vivid sense of re-experiencing at retrieval (e.g., reliving the event with affective and perceptual information, i.e., recollection). Consequently, subjective recollection or "autonoetic" awareness would rely on a relational process (see Klein, 2013).

While several neurobehavioral models were applied to associative memory in adults (see Buchler et al., 2008), its maturation from childhood to early adulthood still needs to be explored in detail. *Within-domain* associative memory was tested in infancy in 9 months old children who were found to encode relations among two items (i.e., a face associated to a specific scenic background), and maintain this relational representation for a few seconds (Richmond and Nelson, 2009). This early developed capacity to bind information continues to improve from 4 to 6 (see Sluzenski et al., 2006; Lloyd et al., 2009 for the learning of item/background associations) and is supposed to reach adult efficiency in middle childhood. In a recent study, Thaler et al. (2013) suggested that long term associative memory, when assessed with an ordered repeated word list paradigm, may plateau from the age of 12 onward.

Other studies have focused on *between-domain* associations, either item/space or item/time respectively. As young as 2 years of age, toddlers are able to retain several item-location associations (Russell and Thompson, 2003) and performances still increase beyond the age of 10 (Barnfield, 1999; Gulya et al., 2002; Hund and Plumert, 2002). Processes of item-location memory may continue to refine until 18–20 years (Lorsbach and Reimer, 2005; see Pirogovsky et al., 2009 for odor-place associations). From 4 years on, children are able to encode temporal parameters that are knowledgeable, i.e., referring to a day. However, it is only later on, around 8 years old, that children can reliably localize multiple events extended into the past (Friedman and Lyon, 2005; Pathman et al., 2013). In sum, the developmental trajectories of associative memory seem to differ according to the component implicated (Picard et al., 2012). Within-domain associative memory dealing with factual information (item/background for instance) may plateau before between-domain associative memory. The maturation of these different types of associative memory may contribute to the development of subjective recollection. Studies that explored subjective experience with Remember/know paradigms reported slight or no modification of familiarity process with age contrary to subjective recollection (Billingsley et al., 2002; Brainerd et al., 2004; Piolino et al., 2007; Ghetti and Angelini, 2008). It is noteworthy that comparisons across developmental studies are challenging due to methodological issues with multiple paradigms and variables that may impact pediatrics behavioral data such as motivational, regulatory, and socio-educational factors.

Complex neurodevelopmental factors account for associative memory evolution from childhood to late adolescence, and can be studied by novel imaging techniques addressing various processes of cerebral maturation (Ghetti and Bunge, 2012). Looking at the cerebral maturation that supports associative memory enhancement from childhood to adolescence, two recent reviews focused on the role of both the prefrontal cortex (PFC) and the hippocampus in such associative processes (Ghetti and Bunge, 2012; Ofen et al., 2012). These two regions show distinct maturational time courses. Overall, PFC maturation appears more prolonged than in other regions (Gogtay et al., 2004). The protracted maturation of the dorsolateral PFC (Giedd, 2004) up to 20 years old seems to be associated with a progressive and late development of top-down attention modulation and strategic processes (Sander et al., 2012). The sparse structural studies that correlated children's performance in standard memory tests with anatomical data provide further evidence that maturational changes in frontal regions [decrease in either cortical thickness (Sowell et al., 2001; Østby et al., 2012) or gray matter volume (Antshel et al., 2008)], are related to increasing memory efficiency in this developmental period. Developmental trends of the hippocampus and their relations with associative memory still need to be clarified.

Because associative memory is a defining feature of episodic memory, the understanding of associative memory development needs to take into consideration the type of associations in order to better describe children's capacity to form and retrieve episodic memories. To date, no behavioral studies have explored the three associative domains (i.e., factual – WHAT, spatial – WHERE, and temporal – WHEN) with a single protocol in the same sample. Thus, the first goal of the present study is to describe the development of within-domain and inter-domain associative memory in a large sample of 160 healthy participants. We further examined our protocol's reliance by confronting these behavioral results to structural imaging data collected in a subgroup of 30 children and adolescents to identify the regions that subserve episodic memory efficiency from childhood to young adulthood. Finally, to consider the possible influence of verbalization and retrieval processes on associative memory efficiency during development, we conducted additional correlational analyses between the 30 participants' performance in verbal fluency and (1) behavioral data (the WHAT-WHERE-WHEN paradigm) and (2) volume of cerebral regions related to associative memory.

MATERIALS AND METHODS

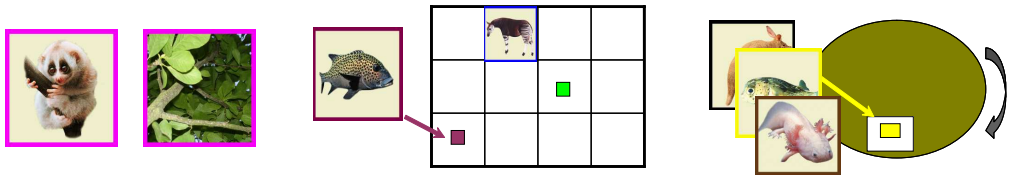
PARTICIPANTS

We conducted the behavioral study on participants aged from 6 to 23 years old recruited among several French Schools, High Schools, and Universities. Exclusion criteria were as follows: history of previous neurological disease, head trauma, current psychoactive medication, and learning disabilities. Families were given a comprehensive description of the research. We obtained written consent from parents of minors, in line with the guidelines of the relevant ethics committees. Informed consent was also obtained from participants over the age of 18. All participants completed the WHAT-WHERE-WHEN episodic memory paradigm (Guillery-Girard et al., 2010). One hundred children from 6 to 10 years (from childhood to adolescence; Mean = 100.7 ± 17.04 months, 51 females) and 60 adolescents and young adults from 12 to 23 years (from adolescence to adulthood; Mean = 194.30 ± 49.90 months, 29 females) were involved in the behavioral study. The children sample had been equally divided among five age groups (each group $n = 20$): 6 years old group (Mean = 77.1 ± 4 months, 11 females), 7 years old group (Mean = 88.7 ± 3.54 months, 12 females), 8 years old group (Mean = 109.5 ± 3.65 months, 12 females), 9 years old group (Mean = 113.2 ± 3.05 months, 7 females), and 10 years old group (Mean = 123.55 ± 3.27 months, 9 females). Similarly, the adolescent and adult sample had been equally divided among three age groups: 11–12 years old group (Mean = 142.55 ± 6.14 months, 10 females), 14–15 years old group (Mean = 180.58 ± 6.77 months, 12 females), and 20–23 years old group (Mean = 259.5 ± 12.86 months, 9 females).

Among these participants, 30 right-handed children and adolescents underwent a morphological MRI [age range: 79–180 months (6.6–15 years), Mean = 135.77 ± 28.19 months (11.31 ± 2.35 years), 13 females]. They additionally participated in various standard neuropsychological tests among which a verbal fluency test (i.e., this French task requires the participants to generate as many words as possible, firstly in a letter fluency condition and secondly, in a category fluency condition – 60 s are provided for each condition). All 30 children and adolescents accurately performed both the behavioral and the morphological MRI investigations on the same day.

Behavioral task

The "WHAT-WHERE-WHEN" paradigm. The WHAT task relied on within-domain factual associations and required participants to learn either 10 (for children aged 6–10 years) or 13 animal-feature associations (11–23) (**Figure 1**). Different list lengths were used to prevent possible ceiling and floor effects for the different age groups (Perez et al., 1998). During the encoding phase, children were shown photographs in a special book with the animal always displayed on the left-hand side and its feature on the right-hand side. Each double page was presented for 5 s (i.e., total encoding time of 50–65 s for the all set of associations). One third of the associations had already been matched and displayed in the book prior to the presentation; another third were to be matched by the experimenter; the remaining third were to be matched by the children themselves. That is, two thirds of the feature photos were laid out in front of the experimenter and the children, at their disposal for them to complete the associations. Color frames were used to emphasize each animal-feature association and to cue children with animal-feature relationship. For instance, photograph of the vicuna displayed in the book was surrounded by a green frame which indicated that its related feature (laid out in the middle of the features set) should be matched according to this color frame. The three different ways of matching the animal and its feature represented three different sources of encoding or "objective recollection" at retrieval. In contrast with intentional encoding of the animal-feature associations, source encoding was deliberately incidental, in order to approach ecological situations as closely as possible. At testing, the children were asked to match the animals with their corresponding features. Thus, the experimenter placed all the features in front of the children, minus their color frame, and provided the animal one at a time. Once, the children matched the feature with the current animal, the experimenter added a second copy of the chosen feature in the set of feature photographs available and removed the photographs of animal-feature association to avoid potential deductions. To assess the subjective recollection that accompanied the retrieval of each animal-feature association, the children were administered the Remember-Know paradigm. This paradigm was adapted for children by using a comic strip comprising three "smiley faces" representing "I remember," "I know," and "I guess" answers. Each type of response was carefully described in order to ensure that children understood every concept. Thus, "I guess" was to be chosen when they were not sure of their answer, while "I know" and "I remember" were to be chosen when children were quite certain. "I know" was then to indicate retrieval of an animal-feature association without any specific details about the encoded episode, "I remember" indicated retrieval of an animal-feature association accompanied by a mental journey back into the past allowing the encoded episode to be relived and phenomenological details retrieved. The difference between Remember and Know was extensively explained to children. To highlight the Remember answers we used a film/video metaphor (i.e., "you remember quite well that they go together because you can see them together like at the first time, as if you were watching a film in which you are the character"). To contrast this with the Know answers, we used a computer metaphor (i.e., "you know quite well that this picture goes with this picture here because they are stored together somewhere in your head, like if they were stored together into a computer"). Specific examples were used to contrast the types of information: their date of birth to refer to personal semantic information and/or the last dance show they attended to refer to personal episodic memories. To ensure children's appropriate use of criteria, they were asked to



WHAT
Participants were asked to encode animal-feature associations.
At testing, children were 1- asked to match animals with their corresponding features,2- they were administered the R/K-G paradigm and 3- asked for the source of encoding (i.e., who performed the association)?

We obtained 4 measures:
WHAT (correct associations)
Objective Recollection (correct sources)
Subjective Recollection (R responses/nb of associations)
Familiarity ((K responses/nb of associations)/1-Subjective Recollection)

WHERE
Participants were asked to encode animal- location associations.
At testing, children were asked to match animals with their corresponding locations.

We obtained 1 measure:
WHERE (correct associations)

WHEN
Participants were asked to encode the sequence of animals.
At testing, children were asked to match animals with their corresponding placement.

We obtained 1 measure:
WHEN (correct placement individually and pairs of animals in the correct temporal order)

Finally, we obtained an **Episodic score** encompassing the three associative memory tests.

FIGURE 1 | «WHAT-WHERE-WHEN»paradigm.

reformulate the instructions. This procedure was adapted to each subject and repeated until the experimenter was confident about the child's understanding of the Remember and Know judgments (see Picard et al., 2009 for a similar approach in autobiographical memory). Finally, for each association, objective recollection was assessed by asking the children to retrieve the corresponding source, in the shape of the person who performed the match (matched by the experimenter; matched by the child or matched prior to the presentation).

The WHERE task relied on between-domain spatial associations and is similar to the sub-test "Memory for designs" from the standardized battery NEPSY II (Korkman et al., 2007). Children were tested on their encoding of the exact location of each animal in an array (3×4 grid for children aged 6–10 years; 4×4 grid for children aged 11–18 years). They encoded the animal-location association by matching the colored frame surrounding the photograph of the animal to a colored marker in the center of each box of the grid. Animals were presented one at a time and the child was asked to place each animal into the correct location. The order of animals presentation was randomized across participants. Animals remained in view as the child proceeded through the task. Once all animals were placed, children were given 1 min to review the animal-location associations. In the test condition, children were again provided with the animals one at a time and were asked to place them in the array. In this condition there were no color cues. Again, animals were randomized across children.

The WHEN task investigated between-domain sequential associative memory. Children were asked to encode the animal-sequence association by placing the animals into slots in a wooden wheel. As the wheel was turned, only one slot was visible at a time. As in the other tasks, the animal-sequence association was determined by color cues that appeared in each slot. Each color corresponded to a specific animal. In the encoding condition, children were provided with the full set of animals and required to place them into the slots following the sequence determined by the color showing in the slot at each turn of the wheel. Once all animals were in place, the children were given one opportunity to review the overall sequence for a maximum of 1 min. In the test condition, children were again provided with the complete set of animals and required to retrieve the exact encoded sequence. Again, there were no color cues in this condition.

The measures derived from the WHAT-WHERE-WHEN test were then as follows:

(i) For the WHAT task: (1) total number of correct animal-feature associations (WHAT); (2) total number of sources that were correctly provided (Objective Recollection); (3) ratio of Remember judgments provided for every accurate association (Subjective Recollection, with Recollection = Remember responses/total number of associations); (4) familiarity is calculated in absence of recollection (as defined by Yonelinas and Jacoby, 1995) with Familiarity = K/1-R, where K = Know responses/total number of associations. This formula allows us to analyze separately Know from Recollection judgments.

(ii) For the WHERE task: total number of correct animal-location associations (WHERE).

(iii) For the WHEN task, we have taken into account both the correct placement of the animals individually and pairs of animals in the correct temporal order (see Riggins et al., 2009 for a similar approach). Thus one point was credited for each animal that was assigned to its rightful place in the sequence and 1/2 point was credited for each animals that accurately followed the original order but were inaccurately placed in the sequence [example A: animal one in first position, animal two in second position, animal three in third position = $(1 + 1 + 1) = 4$ points; example B: animal seven in first position, animal eight in second position, and animal nine in third position = $(2 \times 1/2) = 1$ point]. The WHEN hits thus corresponds to the sum of placement and order in the sequence. We normalized all associative memory scores and Objective Recollection scores. This transformation of these possible heterogeneous raw scores into a common domain is needed prior to combining them into an episodic score (see below) and conducting parametric statistical analysis on normal distributions.

In order to assess overall episodic memory development, we computed a composite score obtained as follow: first, we summed the three z-scores (WHAT, WHERE, and WHEN) for each participant. This score is not quite a z-score, so it has been finally divided by the square root of the sum of the variance of the three subtests (which equals 3×1 since we used z-score) plus twice the sum of the covariance of the three subtests. As they were z-score, their covariances equal their correlation coefficients. For detail, see "Combining different scores from tests" in "Advanced Topics" section of the Psych Assessment website. This score assesses more specifically episodic memory since it encompasses three primary components of associative memory.

$$\text{episodic score} = \frac{Z_{\text{WHAT}} + Z_{\text{WHERE}} + Z_{\text{WHEN}}}{\sqrt{(3 + 2 \times (r_{\text{WHATWHERE}} + r_{\text{WHATWHEN}} + r_{\text{WHEREWHEN}}))}}$$

Imaging data acquisition

3D T1 images were acquired at the UMR663, INSERM, in the Service Hospitalier Frédéric Joliot (CEA-I2BM, Orsay, France), on a 1.5T MRI System (Signa, LX, GEMS, USA), with the following parameters: TR = 9.9 ms; TE = 2 ms; IR-Prep-time = 600 ms; flip angle = 10°; voxel size:0.9 mm × 9 mm × 1.2 mm, acquisition time: 7′56″.

Image processing

MRI data were segmented, normalized to a pediatric sample of the NIH ($N = 324$, age range = 4.5–18.5 years, Fonov et al., 2011), and modulated using the VBM5.1 toolbox (Ashburner and Friston, 2005) implemented in the Statistical Parametric Mapping 5 (SPM) software (Wellcome Trust Centre for Neuroimaging, London, UK) to obtain maps of local gray matter volume corrected for brain size. Finally, each image was smoothed with a Gaussian kernel (FWHM = 12 mm). Furthermore, we used a gray matter explicit mask in the voxelwise analyses so as to restrain the analyses to the gray matter. This mask was obtained by first averaging all segmented gray matter and white matter images, then thresholding

the gray matter average to include voxels with a probability higher than 0.4 and the white matter average to include voxels with a probability higher than 0.2. Finally, the final GM mask used in the analyses was obtained by subtracting the WM mask from the GM mask.

Image statistical analysis

We analyzed age-related changes on brain morphometry using two statistical models entering either age (linear) or age and age2 (quadratic) as predictors using this fitting model: volume $= a0 + a1\text{score} + a2\text{score}^2 + \varepsilon$ where $a0$, $a1$, and $a2$ are polynomial parameters to be found, and error represents the residual error of the model (Büchel et al., 1998; Hu et al., 2013). Finally, we included sex as a regressor of non-interest. In a second set of analyses, each z-score (WHAT, WHERE, and WHEN) and the composite score referring to episodic memory were related to brain morphometry. These analyses were conducted first on the whole brain and second within the hippocampus only using a hippocampus delineated on a template. We performed the same regression analyses as before replacing age by the episodic score. Note that the predictor variables were first orthogonalized before being entered together in the quadratic models: age and age^2 for age-related analyses, episodic and episodic score^2 for brain-behavior relationships analyses. Because any relationship between brain volumes and memory could be driven by the common effect of age or sex, regression analyses with episodic memory were conducted with two regressors of non-interest (age and sex).

Two statistical thresholds were used, one for the whole brain and another for the hippocampus. For the whole brain where widespread effects were expected, we used a statistical threshold of uncorrected $p < 0.001$ and cluster extent $K > 500$ voxels. For analyses focusing on the hippocampus, a less stringent uncorrected p-value cut-off of $p < 0.01$ was applied with a cluster extent $K > 100$ voxels. In this latter condition, more localized effects were expected resulting from developmental differences along the longitudinal axis (DeMaster and Ghetti, 2013).

Complementary analyses

Finally, we conducted a last set of correlations between fluency z-score (which combines both letter and category fluency) and: (1) each z-score (WHAT, WHERE, and WHEN) and the composite score referring to episodic memory, (2) mean of gray matter volumes in clusters previously identified in brain-memory relationships analyses.

RESULTS

BEHAVIORAL RESULTS

Associative memory

We performed one-way ANOVA for each task with age groups as between factor and Tukey's adjustment for multiple comparisons (HSD). Those revealed three different developmental patterns (**Figure 2**).

Childhood to adolescence. First, the one-way ANOVA performed on the WHAT scores revealed a significant group effect [$F(4, 95) = 2.54$; $p = 0.04$] on performance associated with only one significant difference between 6- and 10-year-old groups ($p = 0.04$). These results illustrated a slight but significant increase from 6- to 10-year-olds. Second and considering the WHERE task, we observed a significant and linear increase in performance across age groups [$F(4, 95) = 9.51$; $p < 0.001$; $6 < 8$ and $9 - 7 < 10 - 8 < 10$-year-olds]. Finally, a significant group effect was also found for the WHEN task [$F(4, 95) = 8.33$; $p < 0.001$] with a ceiling effect until the age of 9 followed by a significant increase from 9- to 10-year-olds ($p < 0.001$, **Figure 2A**). This determining period also appeared in the analyses of the episodic scores [$F(4, 95) = 14.56$; $p < 0.001$] that combine the three associative memory tasks (**Figure 2B**). Tuckey *post hoc* tests revealed a slight increase from the age of 6 to 9 followed by a marked increase between 9- and 10-year-olds ($6 < 7, 8, 9$; $10 - 7 < 10 - 8 < 10 - 9 < 10$).

Adolescence to adulthood. The one-way ANOVAs conducted on each of the associative score revealed a significant group effect only for WHERE's performance [$F(2, 57) = 4.74$; $p = 0.01$; $11 - 12 <$ 21–24 age group]. No significant developmental difference was evident for neither the two other associative memory tasks nor the episodic score.

Objective and subjective recollection

Childhood to adolescence. Simple effects analysis conducted on the child groups indicated that the group effect observed on objective recollection [$F(4, 95) = 5.10$; $p < 0.001$] resulted from a significant increase from 8- to 10-year-olds ($6, 7, 8 < 10$, **Figure 2C**). In contrast, the significant group effect on subjective recollection [$F(4, 95) = 6.44$; $p < 0.001$] was related to a slight and linear increase of the ability of remembering (**Figure 2D**).

Adolescence to adulthood. Analysis conducted on the oldest age groups revealed that only the familiarity index decreased significantly from 11–12- to 21–23-year-olds [$F(2, 57) = 3.56$; $p = 0.03$; $11 - 12 >$ 21–24 age group].

IMAGING RESULTS

Age-related effects

The linear regression analysis with total gray matter volume as the dependent variable and age as the predictor variable while controlling for the effect of sex, revealed a statistically significant volume decrease from 6 to 15 years ($R^2 = 0.449$, $p < 0.001$). There was no significant contribution of age^2, when this was included in the regression. Regional analyses revealed significant structural changes mainly in fronto-temporal regions but also involving posterior parietal regions (**Figure 3**). The regression analysis focused on the hippocampus, with the volume as the dependent variable and age as the predictor variable while controlling for the effect of sex, indicate a significant reduction in the volume of the hippocampal body bilaterally extending, in the left hemisphere, to the anterior part of the hippocampus.

Relationships between brain volume and memory performances

Our analyses failed to detect any statistically significant relationship between each z-score independently (i.e., WHAT, WHERE, and WHEN) and gray matter volume. On the contrary, in both whole brain and hippocampus template-based ROI, a quadratic

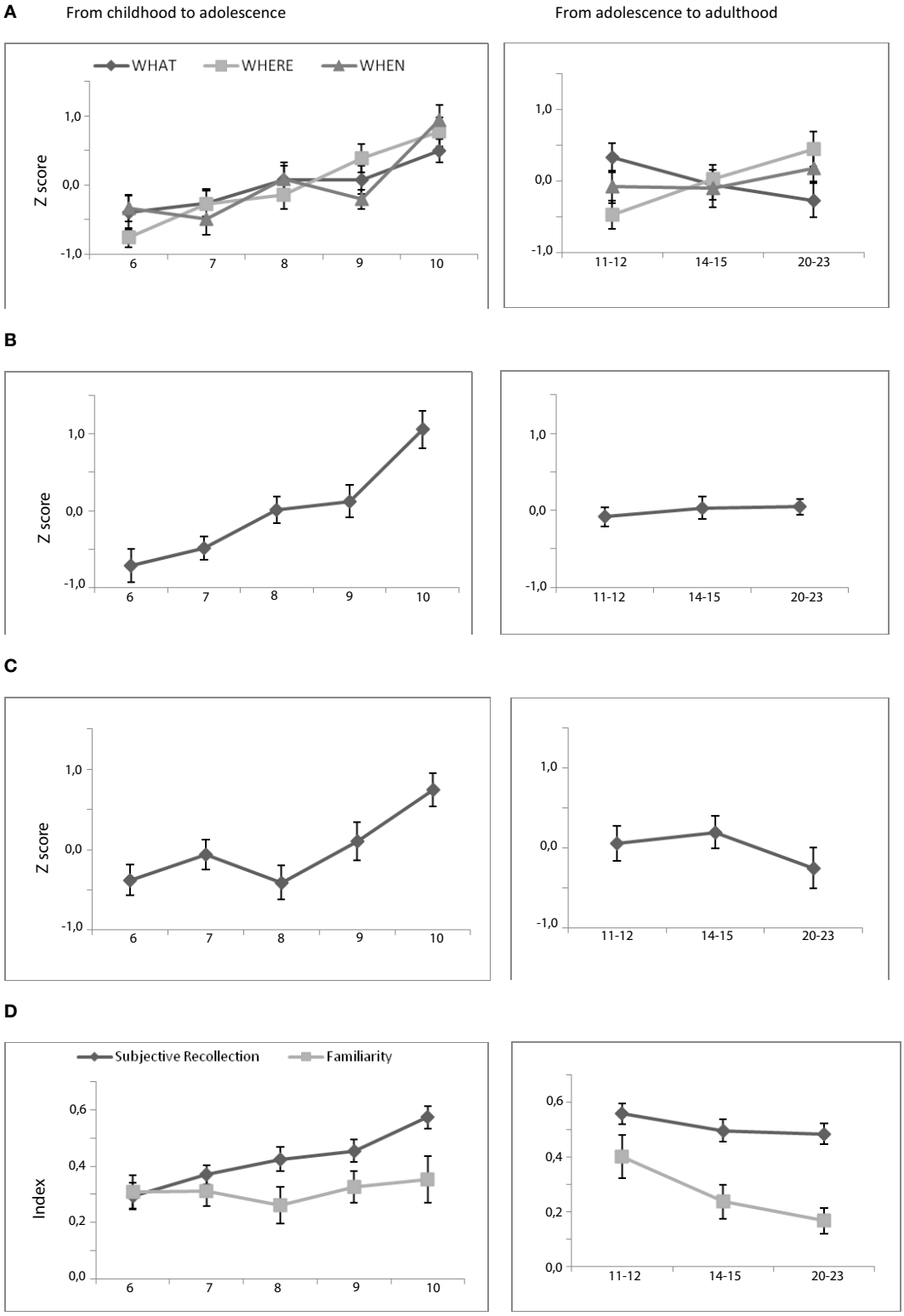


FIGURE 2 | Behavioral performances on the associative memory tasks. **(A)** Mean performance of associative cued recall (hits) for each memory task as a function of age. **(B)** Mean episodic score. **(C)** Mean objective recollection. **(D)** Mean subjective recollection and familiarity index.

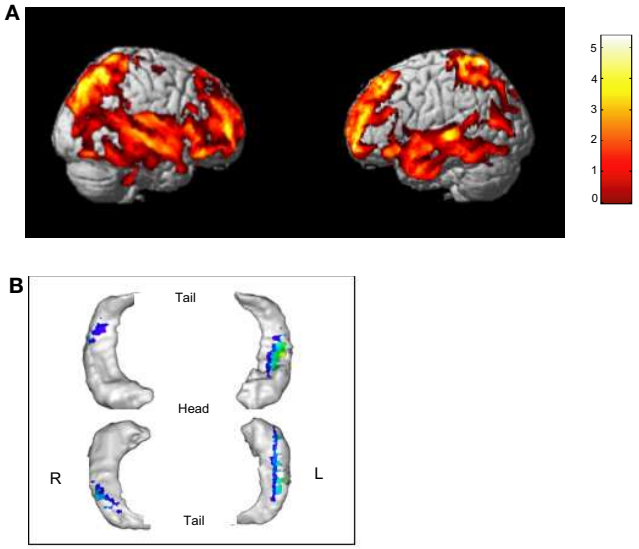


FIGURE 3 | Age-related effects on the brain. **(A)** Age-related changes concern fronto-temporal and posterior parietal regions bilaterally (uncorrected $p < 0.001$, $K > 500$). **(B)** A significant reduction was found in the hippocampus bilaterally, with a more extended region in the left hippocampus (uncorrected $p < 0.01$, $K > 100$).

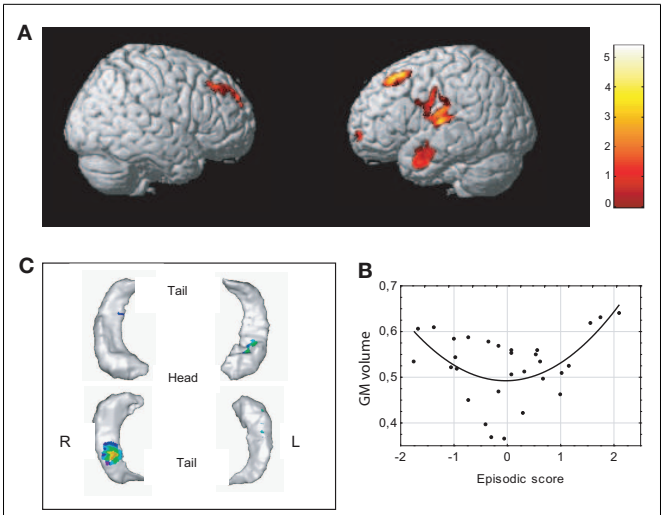


FIGURE 4 | Neural correlates of associative memory. **(A)** Significant positive correlation (quadratic, U-shaped) with episodic score was found with the volume of gray matter in dorsolateral frontal regions bilaterally, the superior temporal cortex, the anterior middle temporal gyrus, and the ventrolateral prefrontal cortex (upper figure, uncorrected $p < 0.001$, $K > 500$). **(B)** Scatterplots of episodic effects are shown for regions identified in whole brain analyses. **(C)** Significant positive correlation (quadratic, U-shaped) was observed between memory and right hippocampal body and the anterior part of the left hippocampus (uncorrected $p < 0.01$, $K > 100$).

positive relation (U-shaped) between volume and episodic score was found. Concerning the whole brain analysis, significant positive correlation with episodic memory was found with the volume of five brain areas in the right hemisphere (**Figure 4**; **Table 1**): (i) dorsolateral frontal regions, including the posterior part of the medial frontal gyrus, (ii) the superior temporal cortex encroaching both the transverse temporal gyrus around the lateral sulcus and the inferior parietal lobule, (iii) the anterior middle temporal gyrus, (iv) the ventrolateral prefrontal cortex (VLPFC) and, (v) the anterior part of dorsolateral PFC. Analyses performed on the hippocampus gray matter volume revealed significant relationships between memory efficiency and the body of the hippocampus on the right side and the anterior part of the hippocampus on the left side. Scatterplots of these effects showed that the enhancement of episodic performances was mainly associated with a decrease in mean volumes except for three participants with the highest scores.

Complementary analyses. Correlational behavioral analyses revealed significant positive correlation between fluency z-score and each associative memory task ($p = 0.004$ WHAT; $p = 0.026$ WHERE; $p = 0.003$ WHEN) and the episodic composite score ($p = 0.003$), indicating that better efficiency in verbal fluency was associated with better performances in associative memory. Also, we observed a significant negative correlation between the fluency z-score and two clusters previously detected, i.e., dorsolateral frontal regions bilaterally and the superior temporal cortex. Thus, a decrease in volume in these three cortical regions was associated with increased efficiency in verbal fluency. These analyses did not detect any statistical correlation with the hippocampus.

Table 1 | Brain – associative memory relationships.

Region		x	y	z	No. voxels	z
WHOLE BRAIN ($p < 0.001$, UNCORRECTED, CLUSTER > 500)						
L	Dorsolateral PF	−17	28	48	2985	4.34
L	Sup temporal	−54	−16	23	4278	4.18
L	Middle temporal	−65	−5	−22	2277	4.14
L	Ventrolateral PF	−38	63	−5	556	3.85
R	Dorsolateral PF	20	45	39	1646	3.71
HIPPOCAMPUS ($p < 0.01$, UNCORRECTED, CLUSTER > 100)						
L	Hippocampus	−34	−17	−20	598	2.92
R	Hippocampus	30	−34	−11	323	2.92

DISCUSSION

The first aim of the present study was to describe the developmental trajectories of associative memory distinguishing within-domain (factual) and between-domain (spatial and temporal) associations by means of an original single paradigm. Results showed that these three types of associative memory follow distinct developmental trajectories: a slight but continuous increase of within-domain factual associative memory (WHAT), a linear increase of between-domain spatial associative memory (WHERE), and noticeable changes in between-domain temporal associative memory from 9 to 10 years (WHEN). Overall, the composite score that combines the three associative components of episodic memory (the "episodic score") showed a slight but significant increase up to 9 years followed by a marked increase from 9 to 10. Regarding recollection, both objective (i.e., source

memory) and subjective recollection improved with age with the most important effects from 8 to 10 years. Hence, these findings highlight major changes from 8–9 to 10 years. Thereafter, adolescence is characterized by slight changes, including enhancement of spatial associative memory and noticeable decrease in familiarity. Voxel-based morphometry suggests that episodic memory performance, which thus relies on remembering WHAT, WHERE, and WHEN components, is related to gray matter volume changes (i.e., following an inverted U-curve) in temporal regions including medial structures, prefrontal, and inferior parietal regions. Although these cortical regions and medial temporal structures have been previously described in functional studies, no such morphological data have been reported in developmental studies in relation with participants' overall associative memory efficiency. Also, our results point out the relevance of using a single paradigm to assess associative memory, source memory, and recollection in order to get a more comprehensive picture of episodic memory development.

DEVELOPMENTAL TRAJECTORIES OF ASSOCIATIVE MEMORY

Consistent with the developmental literature showing a major increase in memory efficiency between 6 and 10 years of age (Jambaqué et al., 1993; Vakil et al., 1998; Waber et al., 2007; Thaler et al., 2013), we found that these three types of associative memory (WHAT, WHERE, and WHEN) jointly improved in school-age children. The associative memory for within-domain features concerning the factual component follows a slight but significant increase from 6 to 10 years. Contrary to Sluzenski et al. (2006), we thus found that associative memory efficiency pursues its developmental course beyond the age of 6. Although the "WHAT" task shares some methodological characteristics with the animal-background associative paradigm proposed by these authors, i.e., to associate an animal with a specific feature, WHAT mainly differs on: (1) the use of a cued recall task known to be more age-sensitive than a recognition task (Picard et al., 2012), (2) the type of features that we designed (i.e., animals' habitat or food), (3) the choice of unfamiliar animals to minimize putative prior semantic knowledge, and (4) the number of targets the participants were asked to remember. Furthermore, the regular increase in performance that we observed until 10 years was followed by a slight (though not significant) decrease during adolescence, which is consistent with previous studies using standard memory tests (Carey et al., 1980; Vakil et al., 1998; Waber et al., 2007). Accordingly, younger children may engage in piecemeal recording whereas older peers may deliberately organize the items to enhance memory efficiency. In adolescence, the enhancement of executive functions and verbal strategies (as assessed here by fluency tasks) may play a critical role in binding mechanisms (see by Rhodes et al., 2011; Picard et al., 2012 for recent data). The impact of the developing executive processes (in line with critical neural changes during adolescence; see Blakemore and Choudhury, 2006) on memory enhancement may explain, at least partially, the great variability in memory performance regularly discussed in the field of developmental neuropsychology (Picard et al., 2012).

In the present study, both spatial and temporal associative memories undergo specific developmental trajectories. Spatial associative memory follows a linear increase that continues from 10 onward. In contrast, we observed a large variability of temporal memory until 9 years followed by a marked increase from 9 to 10, plateauing afterward. These data are thus consistent with the idea that both spatial and temporal memory processes rely on distinct cognitive abilities subserved by distinguishable cerebral networks (Nyberg et al., 1996; Ekstrom and Bookheimer, 2007).

Spatial memory is not a unitary construct and implies peripersonal and extra-personal space processing, both being progressively bound together throughout normal development. These are linked to two different referential frames: allocentric and egocentric. In object-location memory tasks, both would interact with a probable superiority of the allocentric representation allowing individuals to code the location in a relational manner to the surrounding environment (Wang et al., 2005). Previous studies have shown that the type of cues used to remember a location changes from childhood to early adulthood (Bullens et al., 2010, 2011). Allocentric spatial abilities emerge around 2 years of age (Newcombe et al., 1998; Ribordy et al., 2013). However, when experimental designs increase in complexity, performances then depend on additional cognitive functions such as working memory (Lorsbach and Reimer, 2005), mental rotation, and the capacity to understand verbal instructions (Nardini et al., 2006). All these cognitive functions develop through childhood and adolescence and may contribute to the age-related effect on spatial processes observed in the present study from six to early adulthood.

Regarding temporal memory, we observe an abrupt increase in children's performance at the age of nine followed by a plateau from 10 years onward. Memory for the temporal parameters of personal events or experimental items relies on several processes that refer to time (recency and frequency), location (labeling an event with external cues), and relative times of occurrence (sequential memory). The literature acknowledges that sequential memory needs to integrate both the relationship between an item and its position in the sequence and the relationship between two following items. To recollect the actual sequence, one needs to recreate the order in which stimuli were presented, that is to reorganize a set of items according to their temporal relationships. The ability to encode and retrieve sequences is thought to develop gradually from early childhood (McCormack and Hoerl, 1999) to adolescence in tandem with the development of language and organizational skills (Naito, 2003; Romine and Reynolds, 2004). Importantly, many authors support the view that the cognitive components of executive functions are fully efficient around the age of 12 (Anderson, 2002; Huizinga et al., 2006). Effective implementation of executive functions is essential for this kind of reconstructive process to be successful (Friedman and Lyon, 2005). Unexpectedly, we observe a slight, though not significant increase of performance during adolescence. Debriefing of the participants after the test allows us to hypothesize that this results from the particular design of the task itself. Indeed, many adolescents explained that they intentionally created a script on the bases of the animal orders (i.e., "when the urodel runs after the almiqui . . ."). Thus, the use of verbal strategies to encode the sequence in a chronological and meaningful order at this age may impact subsequent retrieval. Interestingly, this is in accordance with our additional analyses showing a significant correlation between verbal fluency efficiency and the WHEN.

Taken together, the above mentioned data suggest that associative episodic memory maturation depends on the type of information to be bound and that the overall processes may differentially contribute to episodic memory enhancement. Accordingly, the evolution of the combining episodic score through childhood tends to be non-linear prompted by the time course of temporal memory. Once more, the period of late childhood (9–10 years of age) is crucial in the developmental time course of episodic memory.

SUBJECTIVE AND OBJECTIVE RECOLLECTION

Objective and subjective recollection have been distinguished in functional (Spaniol et al., 2009 for review) and clinical studies (Duarte et al., 2008) in adults and have more recently encounter an increasing interest in the developmental literature (Ghetti and Angelini, 2008; Picard et al., 2009; Friedman et al., 2010).

In the present study, remember and familiarity judgments were equally distributed in the youngest group but appeared to follow two distinct time courses thereafter. Subjective recollection (as measured by the "remember" responses) showed significant enhancement up to 10 while familiarity remained unchanged during this period. Our findings concerning recollection are thus in accordance with recent data showing that 11 years old children were able to perform like adults (Rhodes et al., 2011). However, in the present study, familiarity judgment slightly decreased during adolescence contrasting with previous published behavioral data reporting no modification of familiarity process with age (Billingsley et al., 2002; Piolino et al., 2007). Yet, functional data sets as collected in Event Related Potential's studies (Friedman et al., 2010) suggested that familiarity is unlikely to be driven by the exact same processes from childhood to late adolescence. The authors notably pointed out the relationship between familiarity and mid-frontal regions recruitment restricted to adolescents. Besides, these data argue for a comprehensive approach based on both neuroimaging and behavioral studies to understand age-related effects on episodic memory maturation.

We deliberately distinguished between subjective and objective recollection. A marked increase in "objective recollection" is reported from early childhood (4–6 years) onward (Perner and Ruffman, 1995; Welch-Ross, 1995) depending on factors such as distinctiveness, frequency, and retention interval (Parker, 1995; Ruffman et al., 2001). Recent data support the idea that objective and subjective recollection improve simultaneously from 6 to 18 years (Ghetti and Angelini, 2008; Ghetti et al., 2011). In the present study, objective (i.e., source memory) and subjective recollection followed slightly different developmental trajectories from 8 to 10 years and seemed more closely connected later on, i.e., from nine to adulthood. This developmental dissociation may be accounted for by difference in processes involved in recollection judgment with possibly preferred perceptual-based analysis in youngest participants (Ofen and Shing, 2013).

RELATIONSHIPS BETWEEN BRAIN VOLUME AND MEMORY EFFICIENCY

The present study pointed out the relationship between an increase in associative memory efficiency and a decrease in gray matter volume in a large cerebral network (including the dorsolateral and VLPFC, superior and anterior temporal regions) and the hippocampus bilaterally. In our sample, only three participants displayed a different pattern. As Shaw et al. (2006) argued in their study on global intellectual efficiency and cortical thickness, in which they reported different developmental trajectories of cortical thickness according to participants' IQs, the variability in our sample may reflect different trajectories depending on the individual level of memory performance.

Frontal regions

Structural maturational changes in frontal lobes, decrease in either cortical thickness (Sowell et al., 2001) or volume (Antshel et al., 2008), are related with enhancement of episodic memory efficiency. Greater activation of lateral PFC was associated with an intentional encoding of scenes, subjective recollection (Ofen et al., 2007; Wendelken et al., 2011), retrieval suppression (Paz-Alonso et al., 2013), contextual memory (Ghetti et al., 2010) in children. However, no functional or structural study was conducted on associative multimodal memory in this population. The only structural study conducted in children and young adults so far indicates that thinner VLPFC may support more efficient relational encoding/retrieval processes of a complex Figure (Østby et al., 2012). In the present study, increased performances were related with volume reduction in the dorsolateral and the VLPFC. Interestingly, the reduction of DLPFC was also correlated with increased performances in verbal fluency in our sample, thus suggesting a possible contribution of executive functions to memory efficiency as measured by the WHAT-WHERE-WHEN paradigm.

Hippocampal structures

Only three other studies have investigated the relationships between memory and medial temporal lobe (Sowell et al., 2001) or hippocampal volume (Yurgelun-Todd et al., 2003; Østby et al., 2012). One reported a positive correlation with consolidation processes while the two other found negative correlations with retrieval performances. Otherwise, longitudinal studies focusing on age-related effects on gray matter volume revealed that the anterior part of the hippocampus decreases in volume from ages 4–25 years (Gogtay et al., 2006). In the present study, a slight decrease in hippocampal volume restricted to the right hippocampal body and the anterior part of the left hippocampus was related to an enhancement of episodic performances. Hence, our results suggest the involvement of a more anterior region in the right hippocampus that would be consistent with a progressive specialization evocated by DeMaster and Ghetti, 2013. However, further investigations are needed to understand the contribution of the hippocampus along its longitudinal axis to the development of episodic memory.

Temporo-parietal region

High-level associative areas allowing the integration of information from several sensory modalities undergo a protracted maturation up to early adulthood (Gogtay et al., 2006). Moreover, they support cognitive processes implicated in episodic memory, working memory updates associated with episodic retrieval (Borst and Anderson, 2013) or recollection (Yonelinas et al., 2005 in adults). The superior temporal gyrus is also implicated into self generation of verbal associations at encoding (Vannest et al., 2012 in

adults). In the present study, we observed that the reduced volume in the superior temporal cortex extending to the inferior parietal lobule was related to episodic enhancement in children and adolescents. This region was not reported in previous structural studies but could support the generation of verbal strategies in our three associative tasks. The negative correlation between the volume reduction in the superior temporal cortex and the increase in verbal fluency performance would be consistent with this hypothesis. Moreover, is this cortical region involved in a larger fronto-parietal network including dorsolateral PFC that would implement cognitive control functions on memory functioning, and would support the progressive development of top-down attention modulation?

METHODOLOGICAL CONSIDERATIONS AND FUTURE DIRECTIONS

Our findings bring interesting perspectives to assess episodic memory from childhood to adolescence in a more comprehensive way. To our knowledge, the present study is the first to address episodic memory maturational trajectories by investigating its main components within the same paradigm. It thus provides a more accurate picture of how episodic memory processes (i.e., binding of within/between-domain information, source memory, recollection, and familiarity) evolve.

By confronting behavioral results to structural data, we also describe the cortical regions that subserve episodic memory efficiency as a whole. Unfortunately, the present study failed to detect finer relationships between each component (factual, spatial, temporal, source memory, or recollection) and brain structures. Knowing the large inter-individual variability in both memory efficiency and cerebral maturation in children and adolescents, we assume that the lack of sensitivity in morphometric analyses could be overcome in a larger cohort.

Taken together, the behavioral and structural analyses questioned the implication of maturing executive processes that may explain, at least partially, the differential trajectories that we report according to the type of information to be encoded and recollected. This hypothesis needs to be directly addressed in a future study by using more dedicated executive tasks.

Besides its relevance to provide additional data to the research literature, the present paradigm is considered to be a sensitive and valid tool to assess episodic memory in the clinical setting. The WHAT-WHERE-WHEN paradigm has been administered to children and adolescents suffering from temporal lobe epilepsy and has successfully detected differential profiles of deficits according to epilepsy lateralization (Guillery-Girard et al., 2010). It thus can be helpful to reveal possible memory dissociations in young patients.

CONCLUSION

Episodic memory refers to the capacity to bind different components into a single representation that will promote a vivid sense of re-experiencing at retrieval. Accordingly, our findings show the differential developmental trajectories of episodic memory processes in relationship with both cortical changes and neuropsychological factors such as verbal strategies and executive functions. Specifically, the present study suggests that the multimodal integration would be related to the maturation of temporal regions and may be modulated by a fronto-parietal network. Despite a limited sample for structural analyses, this study confirms the need to combine neuroimaging and behavioral data in order to better understand the developmental trajectory of episodic memory in a research setting, and to use a single paradigm to assess episodic memory as a whole in a clinical setting.

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REFERENCES

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychol.* 8, 71–82.

Antshel, K. M., Peebles, J., AbdulSabur, N., Higgins, A. M., Roizen, N., Shprintzen, R., et al. (2008). Associations between performance on the Rey-Osterrieth Complex Figure and regional brain volumes in children with and without velocardiofacial syndrome. *Dev. Neuropsychol.* 33, 601–622. doi:10.1080/87565640802254422

Ashburner, J., and Friston, K. J. (2005). Unified segmentation. *Neuroimage* 26, 839–851. doi:10.1016/j.neuroimage.2005.02.018

Barnfield, A. M. (1999). Development of sex differences in spatial memory. *Percept. Mot. Skills* 89, 339–350. doi:10.2466/pms.1999.89.1.339

Billingsley, R. L., Lou Smith, M., and Pat McAndrews, M. (2002). Developmental patterns in priming and familiarity in explicit recollection. *J. Exp. Child Psychol.* 82, 251–277. doi:10.1016/S0022-0965(02)00007-3

Blakemore, S.-J., and Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *J. Child Psychol. Psychiatry* 47, 296–312. doi:10.1111/j.1469-7610.2006.01611.x

Borst, J. P., and Anderson, J. R. (2013). Using model-based functional MRI to locate working memory updates and declarative memory retrievals in the fronto-parietal network. *Proc. Natl. Acad. Sci. U.S.A.* 110, 1628–1633. doi:10.1073/pnas.1221572110

Brainerd, C. J., Holliday, R. E., and Reyna, V. F. (2004). Behavioral measurement of remembering phenomenologies: so simple a child can do it. *Child Dev.* 75, 505–522. doi:10.1111/j.1467-8624.2004.00689.x

Büchel, C., Holmes, A. P., Rees, G., and Friston, K. J. (1998). Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *Neuroimage* 8, 140–148. doi:10.1006/nimg.1998.0351

Buchler, N. G., Light, L. L., and Reder, L. M. (2008). Memory for items and associations: distinct representations and processes in associative recognition. *J. Mem. Lang.* 59, 183–199. doi:10.1016/j.jml.2008.04.001

Bullens, J., Klugkist, I., and Postma, A. (2011). The role of local and distal landmarks in the development of object location memory. *Dev. Psychol.* 47, 1515–1524. doi:10.1037/a0025273

Bullens, J., Nardini, M., Doeller, C. F., Braddick, O., Postma, A., and Burgess, N. (2010). The role of landmarks and boundaries in the development of spatial memory. *Dev. Sci.* 13, 170–180. doi:10.1111/j.1467-7687.2009.00870.x

Carey, S., Diamond, R., and Woods, B. (1980). Development of face recognition: a maturational component? *Dev. Psychol.* 16, 257–269. doi:10.1037/0012-1649.16.4.257

DeMaster, D. M., and Ghetti, S. (2013). Developmental differences in hippocampal and cortical contributions to episodic retrieval. *Cortex* 49, 1482–1493. doi:10.1016/j.cortex.2012.08.004

Duarte, A., Henson, R. N., and Graham, K. S. (2008). The effects of aging on the neural correlates of subjective and objective recollection. *Cereb. Cortex* 18, 2169–2180. doi:10.1093/cercor/bhm243

Ekstrom, A. D., and Bookheimer, S. Y. (2007). Spatial and temporal episodic memory retrieval recruit dissociable functional networks in the human brain. *Learn. Mem.* 14, 645–654. doi:10.1101/lm.575107

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., Collins, D. L., et al. (2011). Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage* 54, 313–327. doi:10.1016/j.neuroimage.2010.07.033

Friedman, D., de Chastelaine, M., Nessler, D., and Malcolm, B. (2010). Changes in familiarity and recollection across the lifespan: an ERP perspective. *Brain Res.* 1310, 124–141. doi:10.1016/j.brainres.2009.11.016

Friedman, W. J., and Lyon, T. D. (2005). Development of temporal-reconstructive abilities. *Child Dev.* 76, 1202–1216. doi:10.1111/j.1467-8624.2005.00844.x-i1

Ghetti, S., and Angelini, L. (2008). The development of recollection and familiarity in childhood and adolescence: evidence from the dual-process signal detection model. *Child Dev.* 79, 339–358. doi:10.1111/j.1467-8624.2007.01129.x

Ghetti, S., and Bunge, S. A. (2012). Neural changes underlying the development of episodic memory during middle childhood. *Dev. Cogn. Neurosci.* 2, 381–395. doi:10.1016/j.dcn.2012.05.002

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., and Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *J. Neurosci.* 30, 9548–9556. doi:10.1523/JNEUROSCI.3500-09.2010

Ghetti, S., Mirandola, C., Angelini, L., Cornoldi, C., and Ciaramelli, E. (2011). Development of subjective recollection: understanding of and introspection on memory states. *Child Dev.* 82, 1954–1969. doi:10.1111/j.1467-8624.2011.01645.x

Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Ann. N. Y. Acad. Sci.* 1021, 77–85. doi:10.1196/annals.1308.009

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U.S.A.* 101, 8174–8179. doi:10.1073/pnas.0402680101

Gogtay, N., Nugent, T. F. III, Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., et al. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus* 16, 664–672. doi:10.1002/hipo.20193

Guillery-Girard, B., Bon, L., Martins, S., Denaveaut, M., Fraboulet, S., and Eustache, F. (2010). "L'évaluation neuropsychologique de la mémoire chez l'enfant," in *Approche Neuropsychologique des Troubles des Apprentissages*, eds S. Chokron, J. F. Démonet, and S. Valdois (Marseille: Solal), 225–247.

Gulya, M., Rossi-George, A., Hartshorn, K., Vieira, A., Rovee-Collier, C., Johnson, M. K., et al. (2002). The development of explicit memory for basic perceptual features. *J. Exp. Child Psychol.* 81, 276–297. doi:10.1006/jecp.2001.2654

Hu, S., Pruessner, J. C., Coupé, P., and Collins, D. L. (2013). Volumetric analysis of medial temporal lobe structures in brain development from childhood to adolescence. *Neuroimage* 74, 276–287. doi:10.1016/j.neuroimage.2013.02.032

Huizinga, M., Dolan, C. V., and van der Molen, M. W. (2006). Age-related change in executive function: developmental trends and a latent variable analysis. *Neuropsychologia* 44, 2017–2036. doi:10.1016/j.neuropsychologia.2006.01.010

Hund, A. M., and Plumert, J. M. (2002). Delay-induced bias in children's memory for location. *Child Dev.* 73, 829–840. doi:10.1111/1467-8624.00441

Jambaqué, I., Dellatolas, G., Dulac, O., Ponsot, G., and Signoret, J. L. (1993). Verbal and visual memory impairment in children with epilepsy. *Neuropsychologia* 31, 1321–1337. doi:10.1016/0028-3932(93)90101-5

Klein, S. B. (2013). Making the case that episodic recollection is attributable to operations occurring at retrieval rather than to content stored in a dedicated subsystem of long-term memory. *Front. Behav. Neurosci.* 7:3. doi:10.3389/fnbeh.2013.00003

Korkman, M., Kirk, U., and Kemp, S. L. (2007). *NEPSY II. Administrative Manual.* San Antonio, TX: Psychological Corporation.

Lloyd, M. E., Doydum, A. O., and Newcombe, N. S. (2009). Memory binding in early childhood: evidence for a retrieval deficit. *Child Dev.* 80, 1321–1328. doi:10.1111/j.1467-8624.2009.01353.x

Lorsbach, T. C., and Reimer, J. F. (2005). Feature binding in children and young adults. *J. Genet. Psychol.* 166, 313–327. doi:10.3200/GNTP.166.3.313-328

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn. Sci. (Regul. Ed.)* 11, 126–135. doi:10.1016/j.tics.2006.12.003

McCormack, T., and Hoerl, C. (1999). Memory and temporal perspective: the role of temporal frameworks in memory development. *Dev. Rev.* 19, 154–182. doi:10.1006/drev.1998.0476

Naito, M. (2003). The relationship between theory of mind and episodic memory: evidence for the development of autonoetic consciousness. *J. Exp. Child Psychol.* 85, 312–336. doi:10.1016/S0022-0965(03)00075-4

Nardini, M., Burgess, N., Breckenridge, K., and Atkinson, J. (2006). Differential developmental trajectories for egocentric, environmental and intrinsic frames of reference in spatial memory. *Cognition* 101, 153–172. doi:10.1016/j.cognition.2005.09.005

Newcombe, N., Huttenlocher, J., Drummey, A. B., and Wiley, J. G. (1998). The development of spatial location coding: place learning and dead reckoning in the second and third years. *Cogn. Dev.* 13, 185–200. doi:10.1016/S0885-2014(98)90038-7

Nyberg, L., McIntosh, A. R., Cabeza, R., Habib, R., Houle, S., and Tulving, E. (1996). General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc. Natl. Acad. Sci. U.S.A.* 93, 11280–11285. doi:10.1073/pnas.93.20.11280

Ofen, N., Chai, X. J., Schuil, K. D. I., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2012). The development of brain systems associated with successful memory retrieval of scenes. *J. Neurosci.* 32, 10012–10020. doi:10.1523/JNEUROSCI.1082-11.2012

Ofen, N., Kao, Y.-C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2007). Development of the declarative memory system in the human brain. *Nat. Neurosci.* 10, 1198–1205. doi:10.1038/nn1950

Ofen, N., and Shing, Y. L. (2013). From perception to memory: changes in memory systems across the lifespan. *Neurosci. Biobehav. Rev.* doi:10.1016/j.neubiorev.2013.04.006

Østby, Y., Tamnes, C. K., Fjell, A. M., and Walhovd, K. B. (2012). Dissociating memory processes in the developing brain: the role of hippocampal volume and cortical thickness in recall after minutes versus days. *Cereb. Cortex* 22, 381–390. doi:10.1093/cercor/bhr116

Parker, J. F. (1995). Age differences in source monitoring of performed and imagined actions on immediate and delayed tests. *J. Exp. Child Psychol.* 60, 84–101. doi:10.1006/jecp.1995.1032

Pathman, T., Larkina, M., Burch, M., and Bauer, P. J. (2013). Young children's memory for the times of personal past events. *J. Cogn. Dev.* 14, 120–140. doi:10.1080/15248372.2011.641185

Paz-Alonso, P. M., Bunge, S. A., Anderson, M. C., and Ghetti, S. (2013). Strength of Coupling within a mnemonic control network differentiates those who can and cannot suppress memory retrieval. *J. Neurosci.* 33, 5017–5026. doi:10.1523/JNEUROSCI.3459-12.2013

Perez, L. A., Peynircioglu, Z. F., and Blaxton, T. A. (1998). Developmental differences in implicit and explicit memory performance. *J. Exp. Child Psychol.* 70, 167–185. doi:10.1006/jecp.1998.2449

Perner, J., and Ruffman, T. (1995). Episodic memory and autonoetic consciousness: developmental evidence and a theory of childhood amnesia. *J. Exp. Child Psychol.* 59, 516–548. doi:10.1006/jecp.1995.1024

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., and Piolino, P. (2012). How do the different components of episodic memory develop? Role of executive functions and short-term feature-binding abilities. *Child Dev.* 83, 1037–1050. doi:10.1111/j.1467-8624.2012.01736.x

Picard, L., Reffuveille, I., Eustache, F., and Piolino, P. (2009). Development of autonoetic autobiographical memory in school-age children: genuine age effect or development of basic cognitive abilities? *Conscious. Cogn.* 18, 864–876. doi:10.1016/j.concog.2009.07.008

Piolino, P., Hisland, M., Ruffeveille, I., Matuszewski, V., Jambaqué, I., and Eustache, F. (2007). Do school-age children remember or know the personal past? *Conscious. Cogn.* 16, 84–101. doi:10.1016/j.concog.2005.09.010

Pirogovsky, E., Murphy, C., and Gilbert, P. E. (2009). Developmental differences in memory for cross-modal associations. *Dev. Sci.* 12, 1054–1059. doi:10.1111/j.1467-7687.2009.00857.x

Rhodes, S. M., Murphy, D., and Hancock, P. J. B. (2011). Developmental changes in the engagement of

episodic retrieval processes and their relationship with working memory during the period of middle childhood. *Br. J. Dev. Psychol.* 29, 865–882. doi:10.1111/j.2044-835X.2010.02014.x

Ribordy, F., Jabès, A., Banta Lavenex, P., and Lavenex, P. (2013). Development of allocentric spatial memory abilities in children from 18 months to 5 years of age. *Cogn. Psychol.* 66, 1–29. doi:10.1016/j.cogpsych.2012.08.001

Richmond, J., and Nelson, C. A. (2009). Relational memory during infancy: evidence from eye tracking. *Dev. Sci.* 12, 549–556. doi:10.1111/j.1467-7687.2009.00795.x

Riggins, T., Miller, N. C., Bauer, P. J., Georgieff, M. K., and Nelson, C. A. (2009). Electrophysiological indices of memory for temporal order in early childhood: implications for the development of recollection. *Dev. Sci.* 12, 209–219. doi:10.1111/j.1467-7687.2008.00757.x

Romine, C. B., and Reynolds, C. R. (2004). Sequential memory: a developmental perspective on its relation to frontal lobe functioning. *Neuropsychol. Rev.* 14, 43–64. doi:10.1023/B:NERV.0000026648.94811.32

Ruffman, T., Rustin, C., Garnham, W., and Parkin, A. J. (2001). Source monitoring and false memories in children: relation to certainty and executive functioning. *J. Exp. Child Psychol.* 80, 95–111. doi:10.1006/jecp.2001.2632

Russell, J., and Thompson, D. (2003). Memory development in the second year: for events or locations? *Cognition* 87, B97–B105. doi:10.1016/S0010-0277(02)00238-X

Sander, M. C., Werkle-Bergner, M., Gerjets, P., Shing, Y. L., and Lindenberger, U. (2012). The two-component model of memory development, and its potential implications for educational settings. *Dev. Cogn. Neurosci.* 2(Suppl. 1), S67–S77. doi:10.1016/j.dcn.2011.11.005

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al. (2006). Intellectual ability and cortical development in children and adolescents. *Nature* 440, 676–679. doi:10.1038/nature04513

Sluzenski, J., Newcombe, N. S., and Kovacs, S. L. (2006). Binding, relational memory, and recall of naturalistic events: a developmental perspective. *J. Exp. Psychol. Learn. Mem. Cogn.* 32, 89–100. doi:10.1037/0278-7393.32.1.89

Sowell, E. R., Delis, D., Stiles, J., and Jernigan, T. L. (2001). Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. *J. Int. Neuropsychol. Soc.* 7, 312–322. doi:10.1017/S135561770173305X

Spaniol, J., Davidson, P. S. R., Kim, A. S. N., Han, H., Moscovitch, M., and Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia* 47, 1765–1779. doi:10.1016/j.neuropsychologia.2009.02.028

Thaler, N. S., Goldstein, G., Pettegrew, J. W., Luther, J. F., Reynolds, C. R., and Allen, D. N. (2013). Developmental aspects of working and associative memory. *Arch. Clin. Neuropsychol.* 28, 348–355. doi:10.1093/arclin/acs114

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Vakil, E., Blachstein, H., and Sheinman, M. (1998). Rey AVLT: developmental norms for children and the sensitivity of different memory measures to age. *Child Neuropsychol.* 4, 161–177. doi:10.1076/chin.4.3.161.3173

Vannest, J., Eaton, K. P., Henkel, D., Siegel, M., Tsevat, R. K., Allendorfer, J. B., et al. (2012). Cortical correlates of self-generation in verbal paired associate learning. *Brain Res.* 1437, 104–114. doi:10.1016/j.brainres.2011.12.020

Waber, D. P., De Moor, C., Forbes, P. W., Almli, C. R., Botteron, K. N., Leonard, G., et al. (2007). The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *J. Int. Neuropsychol. Soc.* 13, 729–746.

Wang, H., Johnson, T. R., Sun, Y., and Zhang, J. (2005). Object location memory: the interplay of multiple representations. *Mem. Cognit.* 33, 1147–1159. doi:10.3758/BF03193219

Welch-Ross, M. K. (1995). An integrative model of the development of autobiographical memory. *Dev. Rev.* 15, 338–365. doi:10.1006/drev.1995.1013

Wendelken, C., Baym, C. L., Gazzaley, A., and Bunge, S. A. (2011). Neural indices of improved attentional modulation over middle childhood. *Dev. Cogn. Neurosci.* 1, 175–186. doi:10.1016/j.dcn.2010.11.001

Yonelinas, A. P., and Jacoby, L. L. (1995). Dissociating automatic and controlled processes in a memory-search task: beyond implicit memory. *Psychol. Res.* 57, 156–165. doi:10.1007/BF00431277

Yonelinas, A. P., Otten, L. J., Shaw, K. N., and Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *J. Neurosci.* 25, 3002–3008. doi:10.1523/JNEUROSCI.5295-04.2005

Yurgelun-Todd, D. A., Killgore, W. D. S., and Cintron, C. B. (2003). Cognitive correlates of medial temporal lobe development across adolescence: a magnetic resonance imaging study. *Percept. Mot. Skills* 96, 3–17. doi:10.2466/pms.2003.96.1.3

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Subjective experience of episodic memory and metacognition: a neurodevelopmental approach

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Episodic retrieval is characterized by the subjective experience of remembering. This experience enables the co-ordination of memory retrieval processes and can be acted on metacognitively. In successful retrieval, the feeling of remembering may be accompanied by recall of important contextual information. On the other hand, when people fail (or struggle) to retrieve information, other feelings, thoughts, and information may come to mind. In this review, we examine the subjective and metacognitive basis of episodic memory function from a neurodevelopmental perspective, looking at recollection paradigms (such as source memory, and the report of recollective experience) and metacognitive paradigms such as the feeling of knowing). We start by considering healthy development, and provide a brief review of the development of episodic memory, with a particular focus on the ability of children to report first-person experiences of remembering. We then consider neurodevelopmental disorders (NDDs) such as amnesia acquired in infancy, autism, Williams syndrome, Down syndrome, or 22q11.2 deletion syndrome. This review shows that different episodic processes develop at different rates, and that across a broad set of different NDDs there are various types of episodic memory impairment, each with possibly a different character. This literature is in agreement with the idea that episodic memory is a multifaceted process.

Keywords: episodic memory, recollection, metamemory, neurodevelopmental disorders

INTRODUCTION

Episodic memory is a system which permits people to retrieve memories characterized by temporal, spatial, and self-referential features. Tulving (1985) characterized episodic memory as "autonoetic" (self-knowing). This state of awareness was related to the recollection of a specific personal context for the retrieved information. From this original description, many different theories have spawned (see reviews from Yonelinas, 2002; Mandler, 2008; Moulin et al., 2013). In experimental settings, recollection is often operationalized as the "recall of information that was experienced during the study episode that is cued by a recognition test stimulus" (Montaldi and Mayes, 2010, p. 1294), and can either be measured by subjective report (e.g., Tulving, 1985) or by objective reports asking the participant to reproduce material from the study phase, such as the source of the information (e.g., DeMaster and Ghetti, 2013). It can be characterized as the retrieval of "something more" – the idea that associated thoughts, feelings, or material from the time of encoding come to mind or can be brought to mind at the time of retrieval (Moulin et al., 2013).

The idea of recollection places great emphasis on operations occurring at retrieval, rather than the content or "type" of memory retrieved (Klein, 2013). Klein et al. (2004) suggested that for memory content to be experienced as episodic at retrieval there are four critical factors: (1) sense of agency, (2) sense of ownership, (3) a capacity for self-reflection, and (4) a sense of time as personal events happening in relation to the self. Such a capacity for reflection is defined as "metacognitive" – the ability to know about one's own mental states. A prominent model of metacognition (Nelson and Narens, 1990) involves two levels of cognitive processes, an exchange of information between a higher order representation and an object level, where mental operations are carried out. Memory proficiency is achieved by the regulation and awareness of the information exchanged between these two levels. In the case of recollection, presumably on-line feelings and thoughts generated during retrieval by the object level are monitored by the meta-level, leading to the implementation of mnemonic strategies, termination of search, and so on.

Retrieval from episodic memory, then, is a complex reflective process. There is a an extremely large literature which points to the complexity of the episodic system, and in healthy adults, a lot is known about the strategic and reflective processes which contribute to effective memory function. Much of this literature

considers metamemory and subjective report. The aim of this review is to set this large literature against what we currently know about episodic memory in children and neurodevelopmental disorders (NDDs). We focus on episodic memory as measured by the recall of rich contextual details and in recollection paradigms (described below). We also present subjective states as measured by first-person experiences of remembering. Finally, to consider strategic and reflective aspects to episodic memory, we consider metamemory function. We start by reviewing healthy development (see Typically Developing Children). The last part of the paper then considers episodic memory, metamemory, and subjective states of episodic memory in NDDs with a neuropsychological approach (see Neurodevelopmental Disorders). In the discussion (see Discussion), we show that this review supports the idea of a fractionation of the episodic memory system and how a developmental approach agree with the idea that there are separable subjective and objective components in episodic memory.

TYPICALLY DEVELOPING CHILDREN

Many studies have now explored children's ability to remember detailed memories and whether this capacity improves throughout childhood and adolescence (see Episodic Memory below). In contrast, the development of the ability to introspect on memory contents (subjective states of recollection) or estimate memory contents (metamemory) has not been explored so often. Because one of the main issues in the subjective experience of memory is the putative difference between recollection and familiarity, we next review these two processes in healthy children (see The Subjective Experience of Memory below). We then develop this emphasis on subjective experiences to take on well-known measures of retrieval failure and metacognitive paradigms such as the feeling of knowing (FOK) (see Metamemory below). Finally, we provide some neuroimaging findings to illustrate the contribution of the brain maturation to the development of episodic memory (see Neurodevelopmental Approach below).

EPISODIC MEMORY

Tulving (2002) suggested that the ability to form episodic memories does not emerge until 4 or 5 years of age (Newcombe et al., 2007; Hayne and Imuta, 2011; Scarf et al., 2013). In fact, several studies show that the ability to form new specific personal events, rich in contextual details, improves during childhood until adolescence (e.g., Brainerd et al., 2004; Ghetti and Angelini, 2008; Howe et al., 2009). For example, Bauer et al. (2012) showed an age-related difference in the development of children's memory for the spatial locations of personal events; older children are more likely to integrate spatial information into their autobiographical memories than younger children.

Many studies now suggest the existence of different developmental trajectories for the different components of episodic memory. In particular, recent studies have shown that familiarity-based processes develop earlier than recollection-based ones (Billingsley et al., 2002; Ghetti and Angelini, 2008; Brainerd et al., 2012). Research has also shown that recalling contextual information develops later than recalling the information itself (Cycowicz et al., 2001, 2003; Pirogovsky et al., 2006). In this context, Sluzenski et al. (2006) showed an age-related improvement in remembering the association between contextual information and factual content between the age of 4 and 6 (see Picard et al., 2012 for similar findings).

THE SUBJECTIVE EXPERIENCE OF MEMORY

Studies exploring developmental changes in the ability to introspect on memory are relatively limited. Research into subjective experience of memory in children has mostly used the Remember/Know paradigm (RK, Tulving, 1985). This requires participants to categorize their responses on a recognition memory test according to whether they *remember* the answer, as opposed to *knowing* it or finding it *familiar*. A first study by Perner and Ruffman (1995) suggested that young children could not reliably differentiate remembering and knowing; children could not judge what originates from personal experience before the age of 3. In a more recent study, Ghetti et al. (2011) also asked children to classify memories into "Remember" or "Familiar" categories. They showed that 6- to 7-year-olds found it difficult to differentiate between states of recollection and familiarity but their level of understanding was nonetheless above chance.

From about the age of 8, children begin to report more experiences of remembering on memory tests, with a developmental trend in the subjective experience of recollection (Billingsley et al., 2002; Ofen et al., 2007; Piolino et al., 2009; Friedman et al., 2010). For example, Billingsley et al. (2002) showed an increase in the proportion of Remember responses with age (from 8 to 19 years), with the youngest group giving fewer correct Remember responses (5% for the youngest group versus 28% for the oldest group). In a more recent study also using the same paradigm, Rhodes et al. (2011) confirmed these findings and suggested that 11-year-olds can engage recollection to the same degree as adults.

Ghetti et al. (2011) explored whether or not the nature of the subjective recollection changed during childhood, and whether the qualitative details of memories changed. In their Experiment 2, children were shown line drawings presented either in red or green. At encoding, they were asked to state aloud the color and were also asked a semantic question. At the retrieval stage, participants reported Remember or Know for each item. This was followed by an old-new recognition decision and a source discrimination judgment (color and question asked). Across all ages, children were more likely to give correct source information to Remember judgments, showing that even young children (e.g., 6- to 7-year-olds) could differentiate between Remember and Familiar judgments. However, young children (before the age of 10) were more likely to wrongly associate correct source with Familiar judgments. Furthermore, older children were more likely to experience subjective recollection when they remembered semantic information. According to Ghetti et al. (2011), this indicates that older children are more aware of the factors which give rise to a feeling of recollection and are more skilled at using that diagnostic information. In other words, children possibly become metacognitively more competent at using source information to support the recollection of a detailed memory. In the next section we follow up this idea, reviewing the scientific literature on metamemory in healthy children.

METAMEMORY

Historically, metamemory has either been investigated from a developmental psychology perspective (see Flavell, 1979) or experimental memory viewpoint (Hart, 1965). The developmental literature has mainly focused on memory strategy and what children know about memory functioning whereas, experimental memory research has generated specific and reliable methods to measure people's ability to introspect on their memory processes (Nelson and Narens, 1990). Recent work has taken these experimental paradigms into developmental populations, uniting these two otherwise disparate approaches to metamemory (for reviews, see Schneider and Lockl, 2002; Lyons and Ghetti, 2010). In this work, experimental paradigms are used in which children are asked to predict their future memory performance either while retrieving the information (e.g., FOK; Hart, 1965; Schacter, 1983; Sacher et al., 2009) or during learning (e.g., Judgment-of-learning, JOL; Arbuckle and Cuddy, 1969). The extent to which children have proficient metamemory is captured in their ability to accurately predict their performance.

In a typical JOL procedure, participants are presented with cue-target pairs and asked to make a JOL reflecting the likelihood that they will later recall the target word when presented with the cue word. Using such a task, Koriat and Shitzer-Reichert (2002) showed a developmental trend, with children becoming more accurate as they get older and thus more able to predict their recall performance. In a typical episodic FOK experiment, participants are presented with word pairs and at test, if they cannot recall the target, they are asked to predict whether they will be able to recognize it later. FOK judgments are thus predictions about the likelihood of subsequent recognition of currently non-recalled information (Hart, 1965; Nelson and Narens, 1990). Using this paradigm, Wojcik et al. (2013a) have showed that children (aged 12) could accurately predict their memory performance when asked to give episodic FOK judgments. However, whether or not a development trend on episodic FOK exists is difficult to determine as most developmental FOK studies have used general knowledge, or pre-learned semantic material. However, such studies do report that FOK accuracy improves continuously across childhood and adolescence (Wellman, 1977; Cultice et al., 1983; Wojcik et al., 2013a, but, see Butterfield et al., 1988).

Other studies exploring the development of metacognitive monitoring have shown that the accuracy of confidence judgments about memory retrieval of individual items improves during late childhood (age 7–12 years; von der Linden and Roebers, 2006; Ghetti et al., 2008; Krebs and Roebers, 2010). Furthermore, young children have a good metacognitive knowledge (Flavell, 1979). Studies have also shown that from a young age children understand some of the factors influencing memory, thus showing metacognitive knowledge (Lyon and Flavell, 1994). For example, Ghetti et al. (2002) showed that children as young as 5 or 6 can monitor varying degrees of memory strength as indicated by changes in their confidence ratings. In a similar vein, two studies have demonstrated that children can accurately use their metacognitive knowledge to make predictions; children assign higher JOLs to judged-easy pairs than to judged-difficult pairs (Koriat and Shitzer-Reichert, 2002; Lockl and Schneider, 2003). Thus children can modulate their JOLs according to their metacognitive knowledge – they are sensitive to the difficulty of to-be-learned material.

Metacognitive judgments such as JOLs or FOKs are important as they will impact on the learning processes and the memory strategies put into place. This is illustrated in the metamemory framework proposed by Nelson and Narens (1990) by the fact that monitoring (the subjective experience) and control processes (the behavior) operate in a feedback loop: through memory monitoring, we control our memory function and implement appropriate mnemonic strategies (the "monitoring affects control hypothesis," Nelson and Leonesio, 1988). As a result, proficient metamemory functioning should ensure effective memory performance. To the best of our knowledge only one study has explored the relationship between monitoring and control from a developmental perspective. Lockl and Schneider (2003) showed that for both first and third graders, JOLs made during the first study trial predicted the amount of time that the children invested in each item in a subsequent self-paced study trial. This relationship between JOL and study time became stronger for third graders (age 9 years).

NEURODEVELOPMENTAL APPROACH

Neuroimaging studies provide evidence that brain maturation contributes to the development of the episodic memory. There is a growing body of evidence showing that major age-related changes occur before puberty with a slight evolution until adulthood focusing mainly on frontal regions (**Figure 1**). These changes include cerebral networks devoted to memory functioning: medial temporal lobe structures, parietal, and frontal regions (Paz-Alonso et al., 2008; Ghetti et al., 2010). There is a complex developmental pattern observed in the connections between frontal and temporal regions, and development of these connections continues into adulthood. Otherwise, the only functional neuroimaging study in children which has focused on subjective recollection evaluated with the RK paradigm points to an age-related increase in activations of the prefrontal cortex (Ofen et al., 2007). Some other studies have revealed a medial temporal specialization with increasing age. Longitudinal studies showed that the anterior hippocampus may decrease relatively in volume from age 4 to 25, while the posterior hippocampus may increase (Gogtay et al., 2006). This structural maturation influences the cerebral network recruited to process episodic memory tasks with age as shown by functional brain imaging studies. For instance, Ghetti et al. (2010) were interested in activations during incidental encoding of items as a function of subsequent memory of items and details associated with target items. Their results revealed that youngest children, aged 8, recruit the hippocampus and posterior parahippocampal gyrus for both item recognition (line drawings) and associated details (color of ink), whereas the 14 years olds engaged these regions only for subsequent detail recollection. Finally, it is worth noting that the medial temporal and prefrontal regions are not the only structures implicated in the development of episodic memory. A graded activation of the posterior parietal cortex is associated with correct episodic performances (Paz-Alonso et al., 2008; Ofen et al., 2012; DeMaster and Ghetti, 2013).

A converging body of arguments also indicates that the posterior parietal cortex is implicated in episodic retrieval and subjective recollection in adults (Shimamura, 2011). The temporo-parietal

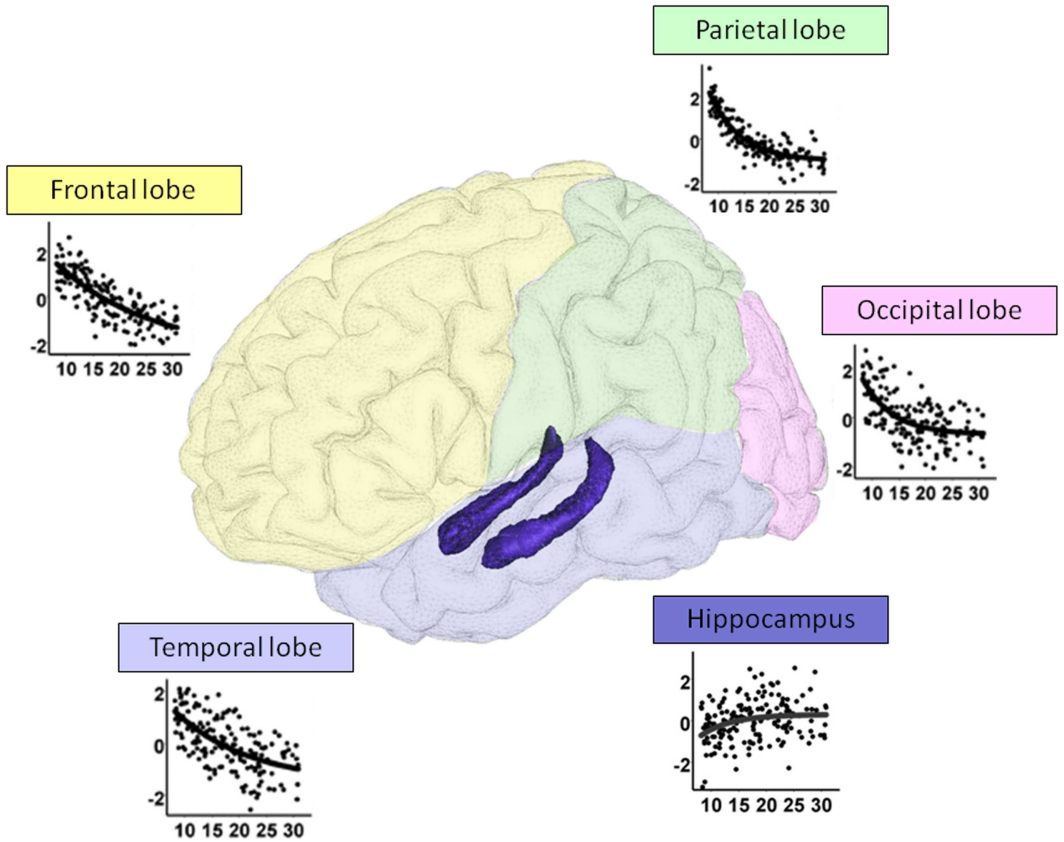


FIGURE 1 | Gray matter maturation from 8 to 30 years: regression plots showing the relationship between age and bilateral cortical volume (corrected for the total brain volume) of each lobe and the hippocampus. The non-linear decrease in cortical lobe volume contrasts with a slight increase in hippocampal volume. Parietal and occipital lobe seem to mature earlier than temporal and frontal lobes. Adapted from Ostby et al. (2009).

junction a one of the cerebral regions referring to the Cortical Medial Structures (CMS) involved in autobiographical memory and critical for self-development (Pfeifer and Peake, 2012). The parietal cortex could also play an important role in mnemonic control by modulating top-down (frontal) and bottom-up (medial temporal structures) processes (Paz-Alonso et al., 2013). Hence, abnormal functioning of one cerebral region included into this network would result in a specific pattern of episodic impairment. This point will be detailed in the following sections.

NEURODEVELOPMENTAL DISORDERS

The cognitive neuropsychological approach to memory function has a long history of using patterns of deficit and dysfunction to better understand and treat memory impairment, but also patient studies yield an important data set by which to evaluate cognitive models and further theories. This review argues that a neuropsychological approach to episodic memory is necessary to understand further the development of episodic memory generally. In this section, studies on NDDs (such as autism or chromosome disorders) are presented to show how these disorders represent an opportunity to better understand the contributions of separate sub-components to episodic memory.

Neurodevelopmental disorders affect neural development with direct consequences on learning. A working definition was proposed by Milan (2013):

> "NNDs are generally accepted to be disorders diagnosed before the age of 18 where: Central nervous system development is impaired and/or delayed, leading to either disruption of discrete cerebral functions, or to generalized impairment across multiple domains" (Milan, 2013, p. 8).

It is possible to further classify disorders according to whether they are genetic (either discrete genetic abnormalities, such as Down syndrome (DS); or multiple anomalies in "polygenic" disorders, such as autism), or acquired (early and congenital brain injuries, such as anoxia). In this review, our drive was to understand more about the processes involved in episodic memory function and dysfunction during development. Rather than being exhaustive in terms of etiology, we organize our review around the key populations which have attracted most attention: amnesia acquired in infancy following anoxia, traumatic brain injury (TBI) or tumors [see Amnesia Acquired in Infancy and Childhood (Anoxia, Traumatic Brain Injury, Brain Tumors)], autism (see Autism), and chromosome disorders (see Williams Syndrome, Down Syndrome, and 22q11.2 Deletion Syndrome).

AMNESIA ACQUIRED IN INFANCY AND CHILDHOOD (ANOXIA, TRAUMATIC BRAIN INJURY, BRAIN TUMORS)

In this section, we present studies of children and adolescents with acquired amnesia due to anoxia, TBI, and brain tumors. **Table 1** presents a summary of the different findings.

Episodic memory studies

The amnesic syndrome is commonly understood to be a profound disorder of episodic memory in association with preserved or relatively preserved short-term memory and general intellectual abilities (Mayes, 1999). Episodic memory deficits can be caused by different factors such as lesions to the bilateral areas of the hippocampus as a result of anoxia, TBI, tumor, or cerebrovascular accident. The first reported case of amnesia with childhood onset is CC (Ostergaard, 1987). CC became amnesic following an anoxic episode at the age of 10 which resulted in multifocal brain damage also involving the hippocampal and parahippocampal regions. While his vocabulary acquisition was far from normal in a 5-year follow up test, he did show some progress suggesting that at least some residual learning took place in the absence of any measurable episodic memory. Broman et al. (1997) reported a 19-year follow up study of a boy who sustained focal hippocampal injury due to an anoxic episode at the age of 8 years; his brain injury severely compromised his episodic memory.

More recently, the episodic deficits in pediatric brain tumor patients have been explored. Brain tumors are the most common solid malignancies in childhood (Saran, 2002). Survivors of brain tumors often acquire complex cognitive difficulties including impairments in attention, processing speed, and different aspects of memory (Palmer et al., 2007). In particular, pediatric neuropsycho-oncology studies reveal clear episodic memory deficits (Guillery-Girard et al., 2004; Martins et al., 2006; Vicari et al., 2007; Svoboda et al., 2010). For example, CL developed severe anterograde amnesia following the surgical removal and subsequent chemo- and radiotherapy treatment of an ependymoma at the age of 4 years (Vicari et al., 2007). CL showed signs of significant memory difficulties in everyday life: she was not able to remember things she was asked to do and where she had put things.

Table 1 | Key findings on episodic memory and metamemory in children and adolescents with anoxia, brain tumor, and traumatic brain injury.

Article/etiology	Age (years)		Main finding
	At injury	At test	
ANOXIA			
Ostergaard (1987)	10 (single case)	15	Residual learning in the absence of measurable episodic memory
Broman et al. (1997)	8 (single case)	27	Severe episodic memory deficits
Vargha-Khadem et al. (1997)	Perinatal (single cases)	14, 19, 22	Profound episodic memory deficit in the context of normal knowledge acquisition during childhood
Baddeley et al. (2001), Düzel et al. (2001)	Perinatal (single case)	23	Jon's recognition memory is selectively supported by familiarity. Difficulty appreciating the difference between *remembering* and *knowing*
Picard et al. (2013)	Perinatal 1 month	18, 19	No sense of recollection associated to bilateral hippocampal atrophy
Rosenbaum et al. (2011)	Perinatal (single case)	20	Greater deficit in recollection than in familiarity
BRAIN TUMOR			
Guillery-Girard et al. (2004) Martins et al. (2006)	3 and 6 (single cases) 6 and 5 (single cases)	10, 11 9.5, 7	Ability to acquire novel semantic concepts despite profound episodic memory deficits
Vicari et al. (2007)	3 (single case)	8	Profound episodic memory deficits with generally preserved semantic memory competencies
Svoboda et al. (2010)	13 (single case)	18	Severe episodic memory impairment with relatively well preserved general intellectual functioning
Pauly-Takacs et al. (2011, 2012)	11 (single case)	14	Profound episodic memory deficit in the context of well preserved premorbid semantic memory and new semantic learning. Lack of insight into own memory processes
TRAUMATIC BRAIN INJURY			
Hanten et al. (2000)	6	11	Verbal learning is within normal limits, but metacognitive predictions are less accurate compared to controls
Hanten et al. (2004)	7	12	Verbal learning and metacognitive monitoring are within normal limits, but ease-of-learning judgments are less accurate compared to controls
Crowther et al. (2011)	10	10–12	Verbal learning and metamemory poorer in children with severe TBI compared to milder forms of TBI and controls

She had difficulties in reporting autobiographical events spanning from the previous few days to years. Similarly, CJ acquired a profound anterograde amnesia following treatment for a rare childhood brain tumor (germinoma) when he was 11 years old (Pauly-Takacs et al., 2011, 2012). CJ experienced particular difficulty retrieving context-rich episodic memories whether they had been encoded before or after the onset of his brain injury. In comparison, his premorbid general knowledge, vocabulary, and autobiographical information were remarkably well preserved. He was able to establish novel semantic facts in laboratory tasks and successfully updated the semantic component of his autobiographical memory in the 5-year period after diagnosis. A series of experiments demonstrated that CJ's amnesia was characterized by a disproportionate deficit in source memory relative to item memory, whereby he permanently failed to accurately report the source or the context of a prior learning episode. Strikingly, his source memory deficit extended to encoding manipulations which enhance learning (e.g., self-generation by imagination). That is, although performance improved with self generation, CJ was no more able to accurately state that a correctly retrieved word had been in an imagination condition or not. This suggests that he was not consciously aware of the benefit in his performance, otherwise the logical response would be to adopt a bias, "if I remember this it must be because I self generated it earlier." Further experiments suggested that CJ's episodic retrieval was severely compromised by his inability to use source information as a basis for conscious recollection – even if this information was retained in memory (Pauly-Takacs, 2012). To date, studies exploring subjective states associated with memory have not yet been introduced to pediatric neuropsycho-oncology.

Vargha-Khadem et al. (2001) proposed the term developmental amnesia (DA) to describe cases who acquired focal bilateral hippocampal pathology very early in life following hypoxic-ischemic episodes (Vargha-Khadem et al., 1997; Gadian et al., 2000). These patients (as adolescents or young adults) presented with a dissociation between episodic and semantic memory. While they had a profound impairment in remembering daily life events, they attended mainstream education where they acquired literacy skills as well as normal levels of intelligence and knowledge. DA is particularly interesting because, as opposed to adult-onset amnesia, there is no well-established prior memory competence that is subsequently lost as a result of a specific brain insult. This led to strong theoretical claims about the functional and neural organization of declarative memory during development. Based on cases of DA, a neuroanatomical model of declarative memory was proposed which postulates that the development of semantic memory depends on parahippocampal cortices but not on the hippocampus, while episodic memory development largely depends on the hippocampus (Vargha-Khadem et al., 1997; Gadian et al., 2000).

In the original description of DA by Vargha-Khadem et al. (2001), the authors suggest a distinction between recollection-based versus familiarity-based judgments. However, studies exploring whether or not children with DA can recall detailed episodic memories and also introspect on these memories are extremely rare. To date, most of the evidence comes from a widely studied case of DA, Patient Jon, who became amnesic as a result of perinatal anoxic episode. The available evidence seems to converge on the conclusion that Jon's recognition memory is selectively supported by familiarity (Baddeley et al., 2001). While Jon readily assigned R responses to a good proportion of correctly recognized items, his justifications for them did not reflect true recollective experience; rather, it appeared that Jon gave "R" judgments when he experienced a sense of ease of access to the items (i.e., fluency as opposed to contextual retrieval) which gave rise to higher confidence in his memory (Baddeley et al., 2001; Gardiner et al., 2008). It was also shown that Jon's recognition memory performance fell significantly below that of controls in tasks where recognition is usually facilitated by recollection specifically (e.g., deeper processing, task-enactment) (Düzel et al., 2001; Gardiner et al., 2008). Finally, at the physiological level, it has been demonstrated that Jon lacks the event-related potential (ERP) index of recollection.

Consistent with the above, a recent assessment employing the Process Dissociation Procedure (PDP; Jacoby, 1991) found that Jon's recognition memory is characterized by intact familiarity but severely compromised recollection (Brandt et al., 2009). In this paradigm, participants complete two different memory tasks, one where they merely have to identify whether or not they have studied the item before, and one where, additionally, they have to specifically declare where or when the item was studied. By comparing performance on the test assessing specifics (which requires recollection) and the test asking for a simple old/new distinction (which merely requires familiarity) it is possible to estimate the separate contributions of familiarity and recollection.

More recently, Picard et al. (2013) explored recollection as measured by the RK paradigm in two cases of DA (Valentine and Jocelyne, both adults who suffered from brain injuries that led to bilateral atrophy of the hippocampus). Both patients' episodic memory was first assessed using the House test (Picard et al., 2012), an ecological test designed to assess what-where-when features coupled with RK judgments. On this task, both patients showed major difficulties, with spatial and temporal context recall at floor. For the RK judgments, Valentine was unable to justify her R responses and Jocelyne could not grasp the difference between Remember and Know judgments, despite clear explanations. Similar difficulties were found when an autobiographical memory was used (TEMPau task, Piolino et al., 2009). Furthermore, the two patients recalled fewer specific autobiographical memories than controls with a clear lack of episodic details (for similar findings, see Kwan et al., 2010). In general, these studies point to a specific recollection deficit in DA. However, the recollection/familiarity dissociation may not always be as clear-cut. Using the R/K paradigm and the ROC procedure, Rosenbaum et al. (2011) reported a case in which *both* recollection and familiarity appeared to be impaired, although there was a trend toward greater deficit in recollection.

Metamemory studies

Of the different etiologies of childhood neuropathology reviewed in this section, children with TBI are the only population where metamemory research using contemporary experimental paradigms has already begun. Considering that axonal injury and focal lesions to frontal cortical areas of the brain are the most common forms of pathology following childhood TBI (Tong et al., 2004), it is probable that disruption to frontally guided networks

such as those supporting recollection and metamemory will be impaired. To the best of our knowledge, only three experimental studies using metamemory judgments in children with TBI have been reported, all by the same research group. Hanten et al. (2000) measured children's metacognitive awareness during a multi-trial verbal learning task. In this study, a small group of children with a mixed level of TBI severity (see **Table 1**) and an age-matched control group were asked to make an Ease of Learning (EOL) and a JOL prediction with respect to their recall performance after a 2-h delay. Contrary to previous reports, Hanten et al., did not find significant differences in recall performance between the TBI and the control group either across the four learning trials or after the delay. However, significant differences were found with respect to the two metamemory measures, such that children with TBI were less accurate at judging the ease with which an item would be learned (EOL) as well as at predicting recall of an item (JOL). In another study, Hanten et al. (2004) tested 37 children with severe and 40 children with mild TBI, and compared their performance to an age-matched control group in the same verbal learning paradigm. Similarly to that found by Hanten et al. (2000), learning and forgetting rates did not differentiate between the groups. With respect to metamemory, all groups tended to overestimate their future recall performance, but children with TBI (i.e., irrespective of severity) did so to a significantly greater degree. Furthermore, the severe group had particular difficulty accurately predicting their performance on the EOL measure. By contrast, no differences were found between the three groups on JOLs suggesting that after gaining experience of the learning task, children with TBI were as able as typically developing children to monitor their learning.

In an attempt to elucidate recovery of memory and metamemory function following childhood TBI, Crowther et al. (2011) classified children with TBI into mild, moderate, and severe groups and considered memory and metamemory performance in a multi-trial verbal learning task across five assessments over a 2 year period. The results indicated that children with moderate and severe TBI showed the greatest improvement across all measures over time, but the performance gap between them and the mild TBI group increased. Contrary to some of the earlier studies with smaller samples, brain injury severity did affect levels of learning across trials in this study. TBI severity was also associated with poorer JOL accuracy.

AUTISM

Autism is a NDD that primarily affects social interaction and communication (American Psychiatric Association, 1994). In this review we present studies including adults and children and report all studies in the **Table 2**.

Episodic memory studies

The "developmental disconnection model" links the symptoms of autism spectrum disorder (ASD) to weak functional connectivity in the brain (Belmonte et al., 2004), and neuroimaging suggests that, for example, deficient self-reflective thought processes (e.g., Theory of Mind) are directly linked to brain abnormalities. A growing literature has also identified memory impairment in autism. Most studies have explored memory in adults with high-functioning autism or Asperger syndrome. Word-pair association learning has been used widely in autism to assess episodic memory (Boucher and Warrington, 1976). Numerous studies have shown that performance on recognition and cued-recall tasks is mostly unimpaired in autism (see Boucher et al., 2012 for a recent review). In fact, research into ASD has only revealed subtle impairments in episodic memory, particularly on free recall tasks of semantically related word lists (see Boucher et al., 2012). Furthermore, no deficits have been reported on semantic memory tasks (Salmond et al., 2005; Bowler et al., 2007; Lind and Bowler, 2009; Wojcik et al., 2013a). Several studies suggest that the memory profile observed in ASD is again linked to abnormalities of the hippocampal formation and other neural regions including the amygdala and the frontal cortex (Boucher et al., 2005; Salmond et al., 2005).

The recollection of children with ASD has been examined with source memory tasks, which might point to a deficit in the retrieval of specifics; an idea which is congruent with the notion that higher order and self-reflective processes are impaired in ASD. Only a very few studies have explored the detail retrieved in ASD (see Bon et al., 2012). The studies report conflicting findings. For example, in a first study, Bennetto et al. (1996) used temporal intrusions as a measure of source memory. Participants (adolescents with ASD and TD controls) were given the California Verbal Learning Test (CVLT; Delis et al., 1987) and the number of intrusions of items from previous lists was measured. It was found that the responses of adolescents with ASD included more intrusions than responses of controls. Participants with ASD also had lower performance when asked to indicate which items had been presented most recently. Using a similar recency task with picture stimuli, Gras-Vincendon et al. (2007) explored this further and found no deficit in adults with ASD. However, Bigham et al. (2010) demonstrated recency judgment impairments in low functioning children/adolescents with ASD. In a more recent study (detailed below), Souchay et al. (2013) showed that adolescents with ASD could recall different types of source information correctly (voice, color, spatial, and temporal localization). However, other studies have suggested that source memory might be more impaired in ASD when the contextual information involves a social aspect, as impairments in social functioning are a primary characteristic of ASD (O'Shea et al., 2005). In other words, it could be that contextual information of the social type is particularly impaired in ASD, mirroring the more fundamentally social nature of this disorder. Furthermore, the recall of contextual information can sometimes be spared alongside an impairment in subjective experience, thus revealing a fractionation of recollection itself. In autism these findings fit well with the brain abnormalities reported in the activation of the default-mode network in autism, and possibly point toward the importance of the self in episodic memory and metamemory functioning (Klein, 2013).

Turning to the RK paradigm, adults with Asperger's syndrome have consistently shown a reduced number of Remember judgments (Bowler et al., 2000a,b, 2007; Tanweer et al., 2010). In a recent study, Souchay et al. (2013) explored subjective states associated with episodic retrieval in adolescents with ASD. The novelty of this study was to measure recollection using objective and subjective methods in the same task. In three different experiments,

Table 2 | Key findings on episodic memory and metamemory in Autism.

Reference	Age (years)	Main finding
Boucher and Warrington (1976)	9 (Exp. 1), 13 (Exp. 2), 12 (Exp. 3), 10 (Exp. 4), 14 (Exp. 5)	Impaired recall and recognition and spared cued recall in ASD
Lind and Bowler (2009)	8	Spared performance on a delayed self-recognition task
Bowler et al. (2007)	33 (Exp1), 33 (Exp. 2), 35 (Exp. 3)	Fewer Remember responses in Asperger syndrome
Gras-Vincendon et al. (2007)	24	Spared memory for temporal context
O'Shea et al. (2005)	10	Impaired source memory for social context
Salmond et al. (2005)	12	Selective episodic memory impairment and preserved semantic memory
Souchay et al. (2013)	14	Spared recollection as tested by objective measures (source memory tasks), but relatively impaired recollection as tested by subjective measures (R/K paradigm)
Bowler et al. (2000a)	29 (Exp. 1 and 2)	Comparable to typical performance on illusory memory task, but memory characterized by a *know*-like rather than *remember*-like profile
Bennetto et al. (1996)	16	Impaired temporal order memory
Tanweer et al. (2010)	34	Poorer recall of AM in Asperger syndrome (AS). Personal memories recalled related to *K* rather than *R* responses
Wilkinson et al. (2010)	13	Inaccurate metacognitive judgments-of-confidence in a face recognition task in children with ASD
Wojcik et al. (2011)	11	Accurate judgment of confidence on a self-performed action task
Wojcik et al. (2013b)	12 (Exp. 1), 13 (Exp. 2)	Spared immediate and delayed judgment-of-learning
Wojcik et al. (2013a)	12	Impaired episodic FOK, spared semantic FOK

the same group of participants was presented with information to learn in a specific context (color and voice in Experiment 1, temporal context in Experiment 2, and spatial context in Experiment 3). At the recognition stage, all participants reported R or K (subjective measure). Furthermore, after the recognition task, they performed a source memory task (objective measure) in which all items presented at encoding were re-presented and participants were asked to recall the source. All three experiments showed that adolescents with ASD could, like Typically Developing controls, correctly recall source information. This suggests that recollection, as measured by the retrieval of contextual information, is preserved in adolescents with ASD. However, recollection as measured by the subjective report, was shown to be impaired, at least in Experiment 1, where the ASD group gave significantly fewer Remember responses than controls. These findings point to a specific and subtle recollection impairment in adolescents with ASD. Souchay et al. (2013) propose that memory in autism, and in particular recollective experience, might be characterized by a lack of rich details related to the self. This interpretation fits with the resting state connectivity studies in autism showing abnormalities of the default-mode network including: the ventral medial prefrontal cortex, the posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsal medial prefrontal cortex, and hippocampal formation (DMN) (Buckner et al., 2008). Several studies have now shown that the DMN plays a putative role in self-referential representations (Buckner et al., 2008), and the implication is that although source information is accessible in ASD it does not give rise to the same experience of remembering, nor is not bound into a whole representation which is re-activated by re-experiencing the event in the past.

Metamemory studies

In autism, studies exploring whether or not children, adolescents, or even adults can reflect metacognitively on their memory and their episodic contents are scarce (see **Figure 2** for a summary). Some research has considered memory confidence, and produced equivocal findings. These judgments-of-Confidence (JOCs), consist of asking participants to estimate the correctness of their answer once they have produced it. Some research points to a deficit in this capacity. For instance, Wilkinson et al. (2010) investigated JOC in children with ASD using a face recognition task – an ability thought to be impaired in autism (e.g., Rouse et al., 2004; Molesworth et al., 2005). After studying 24 face photographs participants carried out a recognition test in which they were presented with 48 photographs and had to recognize the faces presented earlier. Children gave JOCs by reporting whether they were "certain," "somewhat certain," or "guessing" their answers. Memory performance did not vary with the levels of certainty in the ASD group. In short, children with autism did not discriminate between correct and incorrect responses in their confidence judgments. However, Wojcik et al. (2011) showed that children and adolescents with ASD made as accurate JOCs as controls when

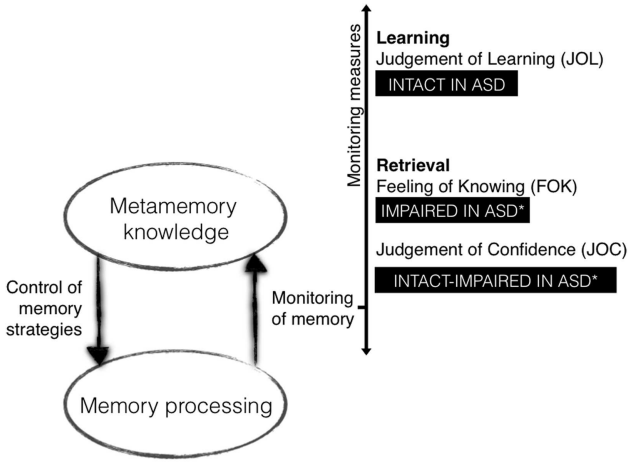


FIGURE 2 | Metamemory findings in autism spectrum disorder.

asked to predict their recall of school-like instructions (e.g., pick up the red ruler and put it in the yellow box, then touch the blue pencil). Thus, studies exploring accuracy of judgments made on information retrieved have revealed contradictory findings, but the extent to which this might relate to the materials in question, or sample differences is not known.

To explore metamemory during encoding, Wojcik et al. (2013b) explored accuracy of JOLs predictions. The aims of this experiment were to see whether participants with ASD would make accurate JOL predictions and also whether JOL accuracy would vary with the time at which JOLs are elicited. Both healthy children (Schneider et al., 2000; Koriat and Shitzer-Reichert, 2002) and adults (Nelson and Dunlosky, 1991) show that delayed JOLs (made some time after study) are far more accurate than immediate JOLs (made immediately after study); this is a robust *delayed JOL effect*. According to Dunlosky and Nelson (1992), this effect occurs because the delayed JOL is based on information which in fact resembles the information retrieved from long-term memory when searching for the target word; thus the effect pertains to the monitoring of episodic processes during retrieval. Wojcik et al. (2013b) presented children with ASD with two separate immediate and delayed JOL tasks. They presented two sets of 24 word pairs at study (e.g., dog-CAR). For the immediate JOL task, after studying each pair they were re-presented with the cue word and asked to make a JOL by predicting whether in about 5 min they would be able to recall the target word when shown the cue word. In the delayed condition, JOLs were given in the same way but after the study of all pairs. The results showed that children with ASD could accurately predict their later recall with both types of JOL, and critically, like TD children they could switch to using more appropriate mnemonic cues. Such an effect arguably demonstrates an ability to use retrieval from memory in order to accurately gage future memory performance, a self-reflective capacity. Finally, Wojcik et al. (2013a) used the episodic FOK (Souchay et al., 2000) paradigm to explore self-reflecting processes at the retrieval stage. Children with ASD were found to give inaccurate episodic FOK judgments in comparison to typical children, suggesting impairment in estimating content at retrieval when information is not easily accessible (the same study showed that semantic FOK was unimpaired).

There are thus conflicting findings in the autism literature, which we have posited might be influenced by the type of information required to make the metamemory judgments. People with ASD may be particularly impaired at the type of reflection captured in feelings of remembering, which we have argued elsewhere are particularly necessary for producing accurate episodic FOK judgments (Souchay et al., 2007; Wojcik et al., 2013a). Of particular interest, the brain network engaged in metamemory (Kikyo et al., 2002; Maril et al., 2003; Kikyo and Miyashita, 2004; Schnyer et al., 2005) and recollection (Yonelinas, 2002; Eichenbaum et al., 2007) shows some overlap with the brain network found underactive in autism. Thus, a decrease in functional activity of these brain networks could lead to some metamemory judgments being inaccurate, such as episodic FOK judgments, and this would presumably have consequences for the regulation and higher order control of episodic memory.

WILLIAMS SYNDROME, DOWN SYNDROME, AND 22Q11.2 DELETION SYNDROME

A recent development in the scientific literature consists of exploring cognition in genetic disorders. Amongst the most explored disorders in children are Williams syndrome (WS), DS, and 22q11.2 deletion syndrome (22q11DS). However, despite the recent growth in this research field, studies exploring episodic memory and metamemory are again scarce in these populations. Furthermore, interpreting the deficits observed relies on our current knowledge of the neural circuits involved in the normal functioning of the memory and the maturation of those specific circuits in these genetic disorders. This section presents a summary of the few studies exploring recollection and subjective states of episodic memory in WS, DS, and 22q11DS and an attempt will be made to link with brain functioning. We report these findings in **Table 3**.

Williams syndrome

Williams syndrome is a relatively rare NDD (prevalence of 1 in 20,000 births) with confirmed genetic origin (random deletion of approximately 25 genes on chromosome 7, specifically 7q11.23; Ewart et al., 1993). Recently this disorder has attracted a great deal of attention due to the unique aspects of social, behavioral, and cognitive deficits. The cognitive profile in WS is characterized by deficits in executive functioning (Rhodes et al., 2010; Carney et al., 2013) and many studies assessing working memory have now demonstrated a dissociation between relatively proficient skills within the verbal domain and more severe impairments associated with visuo-spatial processing (Hoffman et al., 2003; Vicari et al., 2003).

In WS, studies exploring episodic memory are in their infancy. Long-term memory studies have confirmed the dissociation between verbal and visual tasks (Vicari et al., 1996; Edgin et al., 2010). Furthermore, several studies have compared performance in WS in recall and recognition tasks. Jarrold et al. (2007) showed that recall was more impaired than recognition, although Vicari

Table 3 | Key findings on episodic memory and metamemory in children and adolescents with genetic disorders.

Article/etiology	Age (years)	Main finding
WILLIAMS SYNDROME		
Edgin et al. (2010)	18	Deficits in spatial and verbal associative memory compared to individuals with Down syndrome
Costanzo et al. (2013)	20	Reduced recollection and spared familiarity on the process dissociation procedure and task dissociation procedure
Jarrold et al. (2007)	18	Poor performance on long-term memory for visual information
Vicari et al. (1996)	10	Long-term memory deficit on verbal and visual tasks
DOWN SYNDROME		
Edgin et al. (2010)	17	Deficit in associative memory
Carlesimo et al. (1997)	16	Deficit in explicit memory, difficulties in organizing material at encoding, retrieval deficits
Jarrold et al. (2007)	14	Poor performance on long-term memory for visual information
22q11.2 DELETION SYNDROME		
Debbané et al. (2008a)	17	Inefficient recollection-based retrieval, failure to correctly identify contextual information
Debbané et al. (2008b)	14	More source errors, more confusions between exterior sources in which the self was not involved

(2001) reported preserved free recall and recognition of verbal and visual information. It is generally accepted that familiarity has a significant role in recognition but not in free recall, which might point to a deficit in recollection (in recall) but not familiarity (in recognition). However, the conflicting findings in WS regarding recall and recognition are inconclusive. To clarify this issue, Costanzo et al. (2013) explored recollection in WS using two paradigms (PDP and associative recognition) to measure recollection objectively. Results of the two experimental tasks showed a reduced contribution of recollection and a preserved contribution of familiarity. Indeed, the exclusion condition of the PDP task demonstrated that children with WS failed to remember the modality in which the items had been presented whereas the associative recognition task showed that children with WS failed to identify the visual stimulus that had been associated with a target at encoding. According to the authors, these findings suggest that maturation of memory abilities in children with WS is not globally delayed but that instead it shows qualitatively different developmental trajectories. This parallels the observations reported by Meyer-Lindenberg et al. (2005) that the hippocampus in WS shows differences in shape and functioning (reduced resting blood flow in the anterior portion of the hippocampus); deficient hippocampal maturation could potentially underlie poor recollection in WS. Finally, to the best of our knowledge, no study has yet explored subjective states either those associated with retrieval in WS, or the ability to estimate memory as measured by metamemory judgments.

Down syndrome

Down syndrome affects about 1 in 1000 live births (Sherman et al., 2007) and is caused by abnormalities of chromosome 21. In the DS cognitive profile, working memory is typically impaired. People with DS have a deficit in verbal working memory, with non-verbal working memory comparatively preserved, presenting a double dissociation with WS (Baddeley and Jarrold, 2007). More recently, Lanfranchi et al. (2012) showed executive impairment in people with DS. In contrast with multiple studies exploring working memory, only a few studies have explored episodic memory in DS. Carlesimo et al. (1997) showed reduced free recall and reduced recognition in DS. More recently, Edgin et al. (2010) showed reduced associative memory in adolescents with DS on two tasks: a word list learning task (NEPSY list learning test, Korkman et al., 1998) and the spatial Paired Associate Learning (PAL) task from the CANTAB (Sahakian and Owen, 1992). To the best of our knowledge, no study has yet explored recollection, subjective states of episodic memory or metamemory in DS (and this clearly remains a priority). However, a recent single case study exploring autobiographical memory in a 22-year-old male with DS, patient PQ, points to an impairment in recalling detailed memories in DS. Patient PQ's autobiographical memory was characterized by a significantly impoverished recall of specific memories (Robinson and Temple, 2010). Volumetric MRI studies indicate that people with DS have smaller volumes in temporal areas including the hippocampus (Schmidt-Sidor et al., 1990); suggesting that recollection and subjective states of episodic memory might be deficient in DS, but this area still remains to be explored.

22q11.2 deletion syndrome

22q11.2 Deletion syndrome, also known as velo-cardio-facial syndrome (VCFS) is a genetic disorder associated with a microdeletion in chromosome 22q11, estimated to occur in one of every 6000 live births (Botto et al., 2003). Behaviorally, people with 22q11DS also often present with schizophrenia or attention deficit/hyperactivity disorder (ADHD) (see Debbané et al., 2006). A number of studies have explored structural brain differences in 22q11.2DS and these usually report that brain volume in children is between 8 and 11% smaller than controls. Most neuroimaging studies report a total hippocampal volume reduction (Debbané et al., 2006; Kates et al., 2006; Deboer et al., 2007; Flahault et al., 2012). According to Flahault et al. (2012) this reduction of volume could be partly due to a reduction in the amount of input received from connected cortical regions such as the parieto-lateral cortex, the posterior cingulate, and the temporal cortical structures, known also to be reduced in 22q11.2DS.

Little is known about the cognitive characteristics of this syndrome. So far, studies have mainly assessed executive functioning and all report that people with the 22q11DS have marked impairment in visual attention and executive function (Sobin et al.,

2004, 2005). A recent study also showed that differences in brain activation (parietal and occipital regions) explained deficits on a visuo-spatial working memory task (Azuma et al., 2009), thus suggesting that differences in the development of specific brain structures might underpin the cognitive deficits in this population.

Studies exploring episodic memory suggest that people with 22q11.2DS (adolescents and adults) demonstrate similar levels of recognition performance for materials such as words, pictures, or even action statements (Debbané et al., 2008a,b). However, Debbané et al. (2008a) showed in two experiments deficient retrieval skills in adolescents and adults with 22q11.2DS (ages 10–36 years old). In Experiment 1, a directed forgetting paradigm was used (e.g., Bjork, 1970), where participants were instructed to control their encoding according to whether the items were presented as "to be remembered" or "to be forgotten." In Experiment 2, a continuous recognition task was used, in which participants were asked to identify pictures that appeared twice within a list of picture items. In this task, several different lists were used. Participants were instructed to detect repetitions within the list only; items presented in previous lists were to be responded to as novel. In Experiment 1, people with 22q11.2DS were found to produce more false alarms and in Experiment 2 they were found to have more commission errors (higher tendency to incorrectly classify previous list distractors as within list repetitions). The results of Experiment 2 are of particular interest as they suggest that people with 22q11.2DS have specific difficulties in using contextual information (in this case temporal information: current versus past list, paradigm adapted from Schnider and Ptak, 1999) to correctly reject items. According to the authors, these errors might be due to inefficient binding between target and temporal context information and therefore could also point to diminished recollection processes in 22q11.2DS. Deficits in contextual information were also reported by Debbané et al. (2008b) in a source monitoring task in which patients were given action statements and were asked to imagine themselves performing the action or to imagine the experimenter performing the action. Results showed that adolescents with 22q11.2DS committed more source confusion errors than controls. Altogether, these findings thus suggest that recollection, at least as assessed by objective measures (such as source) is impaired in 22q11.2DS.

To the best of our knowledge, no study has yet explored subjective states of episodic memory either using the RK paradigm or metamemory judgment paradigms. However, subjective states of episodic memory as measured by RK are impaired in schizophrenia in that patients with schizophrenia report fewer R responses (Libby et al., 2013) and metamemory has also found to be inaccurate in schizophrenia (Souchay et al., 2006). Therefore, given the behavioral similarities observed with people with 22Q11.2, it seems reasonable to predict impairments in these subjective states or evaluation of memory contents. This remains a priority for future research.

DISCUSSION

The purpose of this article was to review the subjective states associated with episodic retrieval from a neurodevelopmental perspective. This review supports the idea of a fractionation of the episodic memory system and clearly suggests that episodic memory is a multifaceted system as suggested by many theories (Tulving, 2002; Montaldi and Mayes, 2010; Klein, 2013). Within these theories, memory contents are experienced as episodic only if certain operations occur at retrieval, such as retrieval of contextual information or reflective and self-referential processes. This review presented some examples within the developmental literature of dissociations between such processes or different developmental trajectories.

EPISODIC MEMORY IN TYPICALLY DEVELOPING CHILDREN

The first part of this review (see Typically Developing Children), highlighted a developmental change in episodic memory in typically developing children. It is possible to measure separable contributions of a more automatic, perceptual memory system (i.e., familiarity) and a more conceptual higher order system (such as recollection) even at a young age. Clearly however, there are limitations of the episodic memory system in early life. For example, recollection and familiarity are dissociable at about 5 years (Riggins et al., 2013), but recollection processes continue to develop until adulthood. Of particular interest, different developmental trajectories between gist and recollection are found when recollection is measured objectively by contextual details or subjectively by first-person experiences of remembering. As they get older, children report more and more experiences of remembering.

Similarly, increasing evidence suggests that even young children have insight into their memory contents (see Lyons and Ghetti, 2010). Thus, as children develop, they can form and retrieve richer episodic memories and evaluate the content of these memories to guide their learning. This increase in experience of remembering and the formation of rich contextual memories presumably impacts on the development of metamemory. Indeed, a development in the metacognition literature suggests that recollection is used to guide metacognitive judgments (Hicks and Marsh, 2002; Souchay et al., 2007); predictions of future performance are more accurate when contextual information can be retrieved and when there is the feeling of "remembering." We propose then, that the development of richer episodic memories influences the metacognitive assessment of memory content.

Finally, the developmental changes in episodic memory occur alongside the maturation of the brain (see Ghetti and Bunge, 2012; Ofen, 2012 for review). Structural and functional imaging studies suggest a neural specialization with increasing age, such as for example the developmental shift from posterior to anterior hippocampus (see **Figure 2**). The few studies published so far linking brain developmental changes and memory suggest that this brain specialization parallels the development of episodic memory and the development of recollection. The complex network of temporo-frontal structures critical for episodic memory function in healthy adults, and implicated in memory and metamemory disorder in brain-injured populations, include some of the last brain structures to mature. The maturation of brain regions referring to the social brain and CMS has to be taken into consideration when examining the development of subjective recollection. The few studies using social-cognition tasks report an hyperactivation of the CMS in children compared to adults. The same phenomenon is observed in studies of mental-state attribution (Blakemore, 2008). These authors suggested that this decrease in activity from

adolescence to adulthood would be related to an immature or undefined self-appraisal. To better determine how each of these brain structures intersects with the development of the different episodic components, further longitudinal studies are needed. For example, to the best of our knowledge, no study has yet explored the development of metacognitive judgments in relation to neural specialization in children.

EPISODIC MEMORY IN NEURODEVELOPMENTAL DISORDERS

The second part of this review (see Neurodevelopmental Disorders) addressed episodic memory in different NDDs including acquired amnesia, autism, and genetic disorders. This review shows that this strand of research is still in its infancy and that most studies exploring subjective states of episodic memory have been done in children with acquired amnesia and autism whilst such studies are rare in genetic disorders. Despite the novelty of this type of research, the main outcome of these studies is to show that across a broad set of different NDDs there are various types of episodic memory impairment, each with possibly a different character. This literature is thus in agreement with the idea that episodic memory is a multifaceted process (Klein et al., 2004) and that therefore fractionations or dissociations might occur.

Clearly, a child with autism does not present with the same kind of memory deficit as a child with an acquired head injury, but nonetheless they may fail the same episodic memory task, albeit for different reasons. For example, the literature presented here suggests that acquired amnesia is characterized by source memory deficits, whilst in ASD these source memory deficits might be specific to the self. If we can understand the separate contributions to episodic memory impairment implicated in each clinical group in correspondence with their brain damage, we should be able to determine whether a specific brain lesion can affect the development of an episodic component in particular, or if such a lesion will have broader consequences in terms of episodic memory. We will also be better able to compensate for failing mechanisms, and emphasize intact abilities (as has been suggested as an outcome of the metacognition research in autism, for example (Wojcik et al., 2013a).

As an example, consider that Souchay et al. (2013) present a case where a group of people with autism can successfully report the source of an item, but yet, this does not seem to be captured in their subjective experience of remembering. The objective information drawn from recollection, does not seem to be phenomenologically re-experienced in the same way as in controls. In other words, the capacity to retrieve episodic content (source information) could be dissociated from the ability to introspect on the memory content (R responses). Similarly, Wojcik et al. (2013a) showed that a capacity to retrieve memory content (cued recall) was associated with inaccurate introspection (FOK judgments). Interestingly, the dissociations observed in ASD, in some ways resonate with the case of patient R.B. summarized in Klein (2013) presenting a dissociation between memory content (source) and sense of ownership. Here then, we attempt a fractionation of the recollection processes critical to episodic memory function. To attempt such a fractionation, we will have to see episodic memory dysfunction as something rather more nebulous and complex than forgetting (Klein et al., 2004). Recent work suggests that metacognitive judgments and agency judgments are interrelated and thus capture similar processes (Cosentino et al., 2011). Such a relationship would be worth exploring in NDDs to examine this fractionation of episodic memory.

We suggest that to achieve a better understanding of how episodic memory and subjective states of episodic memory develop- and the brain regions involved-further investigations are needed. For example, studies in NDDs could start by exploring whether or not children with NDDs understand the difference between "remembering" and "knowing." Indeed, Jon's case has shown that individuals who grow up without a functional episodic memory system may not be able to appreciate the difference between "remembering" and "knowing." This concern that amnesic patients may not be able to reliably introspect about their own memory processes has been raised in the adult literature as well (Turriziani et al., 2008). This contrasts with the studies in the metamemory literature showing that amnesic patients can predict their memory performance accurately (Janowsky et al., 1989). That is, a fractionation could occur between different subjective states or different ways of introspecting. Introspection (or cognitive monitoring) is crucial to guide strategic behavior (Nelson and Narens, 1990). Thus, other forms of introspection could be explored in children with NDDs, and especially those involved in early strategic behavior such as uncertainty judgments (Lyons and Ghetti, 2013). Neurodevelopmental studies could also assess sense of ownership, agency, and authorship to see if these dissociate from the memory content (see Synofzik et al., 2008 for a theoretical framework to explore agency and ownership). In this context, how the self develops in relationship to episodic memory could be considered through ownership. Indeed, van den Bos et al. (2010) have shown that when participants were asked to sort items into baskets, a self-ownership effect was found on recognition and more for Remember than Know responses. Furthermore, in a more recent study, Cunningham et al. (2013) found that this effect could be used with very young children, thus showing how the self shape memory performance. Such paradigms could be of particular interest to explore in NDDs. Finally, the quality of the episodic contents recalled should also be examined. For example, in adults with Asperger's syndrome, Bowler et al. (2007) showed that the quality of the justifications given to R responses were similar to the ones given by controls, suggesting a difference in quantity and not quality. This issue is particularly important from a developmental perspective and for example in neurogenetic disorders. Do the memory processes just develop later and/or in a qualitatively different manner? Such studies could help us to determine whether or not the content of a memory and the operations occurring at retrieval can be dissociated.

To conclude, we have shown that different episodic processes develop at different rates, and can be dissociated in different clinical groups. In fact it is relatively early in the field to make any strong claims, except that subjective experiences and strategic factors are both critical in the regulation of memory and should therefore be explored further in NDDs. Indeed, where one or other of these processes is impaired or delayed developmentally, there will be consequences in the cognitive system which will be of interest to clinicians and educators working with individuals with neurodevelopmentally disordered groups.

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REFERENCES

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders – (DSM–IV)*, 4th Edn. Washington, DC: American Psychiatric Association.

Arbuckle, T. Y., and Cuddy, L. (1969). Discrimination of item strength at time of presentation. *J. Exp. Psychol.* 81, 126–131. doi:10.1037/h0027455

Azuma, R., Daly, M., Campbel, L., Stevens, A. F., Deeley, Q., Giampietro, V., et al. (2009). Visuospatial working memory in children and adolescents with 2q1.2 deletion syndrome; an fMRI study. *J. Neurodev. Disord.* 1, 46–60. doi:10.1007/s11689-009-9008-9

Baddeley, A., and Jarrold, C. (2007). Working memory and Down syndrome. *J. Intellect. Disabil. Res.* 51, 925–931. doi:10.1111/j.1365-2788.2007.00979.x

Baddeley, A., Vargha-Khadem, F., and Mishkin, M. (2001). Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *J. Cogn. Neurosci.* 13, 357–369. doi:10.1162/08989290151137403

Bauer, P. J., Doydum, A. O., Pathman, T., Larkina, M., Güler, O. E., and Burch, M. (2012). It's all about location, location, location: children's memory for the "where" of personally experienced events. *J. Exp. Child Psychol.* 113, 510–522. doi:10.1016/j.jecp.2012.06.007

Belmonte, M. K., Cook, E. H. Jr., Anderson, G. M., Rubenstein, J. L., Greenough, W. T., Beckel-Mitchener, A., et al. (2004). Autism as a disorder of neural information processing: directions for research and targets for therapy. *Mol. Psychiatry* 9, 646–663.

Bennetto, L., Pennington, B. F., and Rogers, S. J. (1996). Intact and impaired memory functions in autism. *Child Dev.* 67, 1816–1835. doi:10.2307/1131734

Bigham, S., Boucher, J., Mayes, A., and Anns, S. (2010). Assessing recollection and familiarity in autistic spectrum disorders: methods and findings. *J. Autism Dev. Disord.* 40, 878–889. doi:10.1007/s10803-010-0937-7

Billingsley, R. L., Smith, M. L., and McAndrews, M. P. (2002). Developmental patterns in priming and familiarity in explicit recollection. *J. Exp. Child Psychol.* 82, 251–277. doi:10.1016/S0022-0965(02)00007-3

Bjork, R. A. (1970). Positive forgetting: the noninterference of items intentionally forgotten. *J. Verbal Learning Verbal Behav.* 9, 255–268. doi:10.1016/S0022-5371(70)80059-7

Blakemore, S. J. (2008). The social brain in adolescence. *Nat. Rev.* 9, 267–277. doi:10.1038/nrn2353

Bon, L., Baleyte, J.-M., Piolino, P., Desgranges, B., Eustache, F., and Guillery-Girard, B. (2012). Growing up with Asperger's syndrome: developmental trajectory of autobiographical memory. *Front. Psychol.* 3:605. doi:10.3389/fpsyg.2012.00605

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., et al. (2003). A population-based study of the 22q11,2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics* 112, 101–107. doi:10.1542/peds.112.1.101

Boucher, J., Mayes, A., and Bigham, S. (2012). Memory in autistic spectrum disorder. *Psychol. Bull.* 138, 458–496. doi:10.1037/a0026869

Boucher, J., Mayes, A., Cowell, P., Broks, P., Farrant, A., and Roberts, N. A. (2005). A combined clinical, neuropsychological and neuroanatomical study of adults with high functioning autism. *Cogn. Neuropsychiatry* 10, 165–214. doi:10.1080/13546800444000038

Boucher, J., and Warrington, E. (1976). Memory deficits in early infantile autism: some similarities to the amnesic syndrome. *Br. J. Psychol.* 67, 73–87. doi:10.1111/j.2044-8295.1976.tb01499.x

Bowler, D. M., Gardiner, J. M., and Gaigg, S. B. (2007). Factors affecting conscious awareness in the recollective experience of adults with Asperger's syndrome. *Conscious. Cogn.* 16, 124–143. doi:10.1016/j.concog.2005.12.001

Bowler, D. M., Gardiner, J. M., and Grice, S. J. (2000a). Episodic memory and remembering in adults with Asperger's syndrome. *J. Autism Dev. Disord.* 30, 295–304. doi:10.1023/A:1005575216176

Bowler, D. M., Gardiner, J. M., Grice, S., and Saavalainen, P. (2000b). Memory illusions: false recall and recognition in adults with Asperger's syndrome. *J. Abnorm. Psychol.* 109, 663–672. doi:10.1037/0021-843X.109.4.663

Brainerd, C. J., Aydin, C., and Reyna, V. F. (2012). Development of dual-retrieval processes in recall: learning, forgetting, and reminiscence. *J. Mem. Lang.* 66, 763–788. doi:10.1016/j.jml.2011.12.002

Brainerd, C. J., Holliday, R. E., and Reyna, V. F. (2004). Behavioral measurement of remembering phenomenologies: so simple a child can do it. *Child Dev.* 75, 505–522. doi:10.1111/j.1467-8624.2004.00689.x

Brandt, K. R., Gardiner, J. M., Vargha-Khadem, F., Baddeley, A. D., and Mishkin, M. (2009). Impairment of recollection but not familiarity in a case of developmental amnesia. *Neurocase* 15, 60–65. doi:10.1080/13554790802613025

Broman, M., Rose, A. L., Hotson, G., and McCarthy Casey, C. M. (1997). Severe anterograde amnesia with onset in childhood as a result of anoxic encephalopathy. *Brain* 120, 417–433. doi:10.1093/brain/120.3.417

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi:10.1196/annals.1440.011

Butterfield, E. C., Nelson, T. O., and Peck, V. (1988). Developmental aspects of the feeling of knowing. *Dev. Psychol.* 24, 654–663.

Carlesimo, G. A., Marotta, L., and Vicari, S. (1997). Long-term memory in mental retardation: evidence for a specific impairment in subjects with Down's syndrome. *Neuropsychologia* 35, 71–79. doi:10.1016/S0028-3932(96)00055-3

Carney, D. P. J., Brown, J., and Henry, L. (2013). Executive function in Williams syndrome and Down syndromes. *Res. Dev. Disabil.* 34, 46–55. doi:10.1016/j.ridd.2012.07.013

Cosentino, S., Metcalfe, J., Holmes, B., Steffener, J., and Stern, Y. (2011). Finding the self in metacognitive evaluations: metamemory and agency in nondemented elders. *Neuropsychology* 25, 602–612. doi:10.1037/a0023972

Costanzo, F., Vicari, S., and Carlesimo, G. (2013). Familiarity and recollection in Williams syndrome. *Cortex* 49, 232–242. doi:10.1016/j.cortex.2011.06.007

Crowther, J. E., Hanten, G., Li, X., Dennis, M., Chapman, S. B., and Levin, H. S. (2011). Impairments in learning, memory, and metamemory following childhood head injury. *J. Head Trauma Rehabil.* 26, 192–201. doi:10.1097/HTR.0b013e318218dd22

Cultice, J., Somerville, S., and Wellman, H. (1983). Preschoolers' memory monitoring: feeling-of-knowing judgments. *Child Dev.* 54, 1480–1486. doi:10.2307/1129810

Cunningham, S. J., Vergunst, F., Macrea, C. N., and Turk, D. J. (2013). Exploring early self-referential memory effects through ownership. *Br. J. Dev. Psychol.* 31, 289–301. doi:10.1111/bjdp.12005

Cycowicz, Y. M., Friedman, D., and Duff, M. (2003). Pictures and their colors: what do children remember? *J. Cogn. Neurosci.* 15, 759–768. doi:10.1162/jocn.2003.15.5.759

Cycowicz, Y. M., Friedman, D., Snodgrass, J. G., and Duff, M. (2001). Recognition and source memory for pictures in children and adults. *Neuropsychologia* 39, 255.267. doi:10.1016/S0028-3932(00)00108-1

Debbané, M., Glaser, B., and Eliez, S. (2008a). Encoding and retrieval processes in velo-cardio-facial syndrome (VCFS). *Neuropsychology* 22, 226–234. doi:10.1037/0894-4105.22.2.226

Debbané, M., Van der Linden, M., Glaser, B., and Eliez, S. (2008b). Source monitoring for actions in adolescents with 22q11.2 deletion syndrome. *Psychol. Med.* 38, 811–820. doi:10.1017/S003329170700222X

Debbané, M., Schaer, M., Farhoumand, R., Glaser, B., and Eliez, S. (2006). Hippocampal volume reduction in 22q11.2 deletion syndrome. *Neuropsychologia* 44, 2360–2365. doi:10.1016/j.neuropsychologia.2006.05.006

Deboer, T., Wu, Z., Lee, A., and Simon, T. J. (2007). Hippocampal volume reduction in children with chromosome 22q11.2 deletion syndrome is associated with cognitive impairment. *Behav. Brain Funct.* 3, 54. doi:10.1186/1744-9081-3-54

Delis, D., Kramer, J., Kaplan, E., and Ober, B. (1987). *California Verbal Learning Test.* San Antonio, TX: The Psychological Corporation.

DeMaster, D. M., and Ghetti, S. (2013). Developmental differences in hippocampal and cortical contributions to episodic retrieval. *Cortex* 49, 1482–1493. doi:10.1016/j.cortex.2012.08.004

Dunlosky, J., and Nelson, T. O. (1992). Importance of the kind of cue for judgments for learning (JOL) and the delayed-JOL effect. *Mem. Cognit.* 20, 374–380.

Düzel, E., Vargha-Khadem, F., Heinze, H. J., and Mishkin, M. (2001). Brain activity evidence for recognition without recollection after early hippocampal damage. *Proc. Natl. Acad. Sci. U.S.A.* 98, 8101–8106. doi:10.1073/pnas.131205798

Edgin, J., Pennington, B., and Mervis, C. (2010). Neuropsychological components of intellectual disability: the contributions of immediate, working, and associative memory. *J. Intellect. Disabil. Res.* 54, 406–417. doi:10.1111/j.1365-2788.2010.01278.x

Eichenbaum, H., Yonelinas, A. R., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152. doi:10.1146/annurev.neuro.30.051606.094328

Ewart, A. K., Morris, C. A., Atkinson, D., Jin, W., Sternes, K., Spallone, P., et al. (1993). Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat. Genet.* 5, 11–16.

Flahault, A., Schaer, M., Ottet, M. C., Debbané, M., and Eliez, S. (2012). Hippocampal volume reduction in chromosome 22q11.2 deletion syndrome (22q11.2DS): a longitudinal study of morphometry and symptomatology. *Psychiatry Res.* 203, 1–5. doi:10.1016/j.pscychresns.2011.09.003

Flavell, J. H. (1979). Metacognition and cognitive monitoring: a new area of cognitive-developmental inquiry. *Am. Psychol.* 34, 906–911. doi:10.1037/0003-066X.34.10.906

Friedman, D., de Chastelaine, M., Nessler, D., and Malcolm, B. (2010). Changes in familiarity and recollection across the lifespan: an ERP perspective. *Brain Res.* 1310, 124–141. doi:10.1016/j.brainres.2009.11.016

Gadian, D. G., Aicardi, J., Watkins, K. E., Porter, D. A., Mishkin, M., and Vargha-Khadem, F. (2000). Developmental amnesia associated with early hypoxic-ischemic injury. *Brain* 123, 429–507. doi:10.1093/brain/123.3.499

Gardiner, J. M., Brandt, K. R., Baddeley, A. D., Vargha-Khadem, F., and Mishkin, M. (2008). Charting the acquisition of semantic knowledge in a case of developmental amnesia. *Neuropsychologia* 46, 2865–2868. doi:10.1016/j.neuropsychologia.2008.05.021

Ghetti, S., and Angelini, L. (2008). The development of recollection and familiarity in childhood and adolescence: evidence from the dual-process signal detection model. *Child Dev.* 79, 339–358. doi:10.1111/j.1467-8624.2007.01129.x

Ghetti, S., and Bunge, S. A. (2012). Neural changes underlying the development of episodic memory during middle childhood. *Dev. Cogn. Neurosci.* 2, 381–395. doi:10.1016/j.dcn.2012.05.002

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., and Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *J. Neurosci.* 30, 9548–9556. doi:10.1523/JNEUROSCI.3500-09.2010

Ghetti, S., Lyons, K. E., Lazzarin, F., and Cornoldi, C. (2008). The development of metamemory monitoring during retrieval: the case of memory strength and memory absence. *J. Exp. Child Psychol.* 99, 157–181. doi:10.1016/j.jecp.2007.11.001

Ghetti, S., Mirandola, C., Angelini, L., Corndoli, C., and Ciaramelli, E. (2011). Development of subjective recollection: understanding of and introspection on memory states. *Child Dev.* 82, 1954–1969. doi:10.1111/j.1467-8624.2011.01645.x

Ghetti, S., Qin, J. J., and Goodman, G. S. (2002). False memories in children and adults: Age, distinctiveness, and subjective experience. *Dev. Psychol.* 38, 705–718. doi:10.1037/0012-1649.38.5.705

Gogtay, N., Nugent, T. F. III, Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., et al. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus* 16, 664–672. doi:10.1002/hipo.20193

Gras-Vincendon, A., Mottron, L., Salame, P., Bursztejn, C., and Danion, J. (2007). Temporal context memory in high-functioning autism. *Autism* 11, 523–534. doi:10.1177/1362361307083257

Guillery-Girard, B., Martins, S., Parisot, D., and Eustache, F. (2004). Semantic acquisition in childhood amnesic syndrome: a prospective study. *Neuroreport* 15, 377–381. doi:10.1097/00001756-200402090-00033

Hanten, G., Bartha, M., and Levin, H. S. (2000). Metacognition following pediatric traumatic brain injury. *Dev. Neuropsychol.* 18, 383–398. doi:10.1207/S1532694206Hanten

Hanten, G., Dennis, M., Zhang, L., Barnes, M., Roberson, G., Archibald, J., et al. (2004). Childhood head injury and metacognitive processes in language and memory. *Dev. Neuropsychol.* 25, 85–106. doi:10.1207/s15326942dn2501\&2_6

Hart, J. T. (1965). Memory and the feeling-of-knowing experiments. *J. Educ. Psychol.* 56, 208–216. doi:10.1037/h0022263

Hayne, H., and Imuta, K. (2011). Episodic memory in 3- and 4-year-old children. *Dev. Psychobiol.* 53, 317–322. doi:10.1002/dev.20527

Hicks, J. L., and Marsh, R. L. (2002). On predicting the future states of awareness for recognition of unrecallable items. *Mem. Cognit.* 30, 60–66.

Hoffman, J. E., Landau, B., and Pagani, B. (2003). Spatial breakdown in spatial construction: evidence from eye fixations in children with Williams syndrome. *Cogn. Psychol.* 46, 260–301. doi:10.1016/S0010-0285(02)00518-2

Howe, M., Courage, M., and Rooksby, M. (2009). "The genesis and development of autobiographical memory," in *The Development of Memory in Infancy and Childhood*, 2nd Edn, eds M. L. Courage and N. Cowan (Hove: Psychology Press), 177–196.

Jacoby, L. (1991). A process dissociation framework: separating automatic from intentional influences of memory. *J. Mem. Lang.* 30, 513–554. doi:10.1016/0749-596X(91)90025-F

Janowsky, J. S., Shimamura, A. P., and Squire, L. R. (1989). Memory and metamemory: comparisons between patients with frontal lobe lesions and amnesic patients. *Psychobiology* 17, 3–11.

Jarrold, C., Baddeley, A. D., and Phillips, C. (2007). Long-term memory for verbal and visual information in Down syndrome and Williams syndrome: performance on the doors and people test. *Cortex* 43, 233–247. doi:10.1016/S0010-9452(08)70478-7

Kates, W. R., Miller, A. M., Abdulsabur, N., Antshel, K. M., Conchelos, J., Fremont, W., et al. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *J. Am. Acad. Child Adolesc. Psychiatry* 45, 587–595. doi:10.1097/01.chi.0000205704.33077.4a

Kikyo, H., and Miyashita, Y. (2004). Temporal lobe activations of "feeling-of-knowing" induced by face-name associations. *Neuroimage* 23, 1348–1357. doi:10.1016/j.neuroimage.2004.08.013

Kikyo, H., Ohki, K., and Miyashita, Y. (2002). Neural correlates for feeling-of-knowing: an fMRI parametric analysis. *Neuron* 36, 177–186. doi:10.1016/S0896-6273(02)00939-X

Klein, S. B. (2013). Making the case that episodic recollection is attributable to operations occurring at retrieval rather than to content stored in a dedicated subsystem of long-term memory. *Front. Behav. Neurosci.* 7:3. doi:10.3389/fnbeh.2013.00003

Klein, S. B., German, T. P., Cosmides, L., and Gabriel, R. (2004). A theory of autobiographical memory: necessary components and disorders resulting from their loss. *Soc. Cogn.* 22, 460–490. doi:10.1521/soco.22.5.460.50765

Koriat, A., and Shitzer-Reichert, R. (2002). "Metacognitive judgments and their accuracy: insights from the processes underlying judgments of learning in children," in *Metacognition: Process, Function, and Use*, eds P. Chambres, M. Izaute, and P.-J. Marescaux (New York, NY: Kluwer), 1–17.

Korkman, M., Kirk, U., and Kemp, S. (1998). *NEPSY: A Developmental Neuropsychological Assessment.* San Antonio, TX: The Psychological Corporation.

Krebs, S. S., and Roebers, C. M. (2010). Children's strategic regulation, metacognitive monitoring and control processes during test taking. *Br. J. Educ. Psychol.* 80, 325–340. doi:10.1348/000709910X485719

Kwan, D., Carson, N., Addis, D. R., and Rosenbaum, R. S. (2010). Deficits in past remembering extend to future imagining in a case of developmental amnesia. *Neuropsychologia* 48, 3179–3186. doi:10.1016/j.neuropsychologia.2010.06.011

Lanfranchi, S., Baddeley, A., Gathercole, S., and Vianello, R. (2012). Working memory in Down syndrome: is there a dual task deficit? *J. Intellect. Disabil. Res.* 56, 157–166. doi:10.1111/j.1365-2788.2011.01444.x

Libby, L. A., Yonelinas, A. P., Ranganath, C., and Ragland, J. D. (2013). Recognition and familiarity in schizophrenia: a quantitative review. *Biol. Psychiatry* 73, 944–950. doi:10.1016/j.biopsych.2012.10.027

Lind, S. E., and Bowler, D. M. (2009). Delayed self-recognition in autism spectrum disorder: evidence for impaired temporally extended self-awareness? *J. Autism Dev. Disord.* 39, 643–650. doi:10.1007/s10803-008-0670-7

Lockl, K., and Schneider, W. (2003). Metakognitive Überwachungs- und Selbstkontrollprozesse bei der Lernzeiteinteilung von Kindern. [Metacognitive monitoring and self-control processes for children's allocation of study time.]. *Z. Entwicklungspsychol. Padagog. Psychol.* 17, 173–183. doi:10.1024//1010-0652.17.34.173

Lyon, T. D., and Flavell, J. H. (1994). Young children's understanding of "remember" and "forget". *Child Dev.* 65, 1357–1371. doi:10.2307/1131503

Lyons, K., and Ghetti, S. (2010). "Metacognitive development in early childhood: new research challenges, old assumptions," in *Trends and Prospects in Metacognition Research*, eds A. Efklides and P. Misailidi. Hauppauge, NY: Nova Publishers.

Lyons, K., and Ghetti, S. (2013). I don't want to pick: introspection on uncertainty supports early strategic behavior. *Child Dev.* 84, 726–736. doi:10.1111/cdev.12004

Mandler, G. (2008). Familiarity breeds attempts: a critical review of dual-process theories of recognition. *Perspect. Psychol. Sci.* 3, 390–399. doi:10.1111/j.1745-6924.2008.00087.x

Maril, A., Simons, J. S., Mitchell, J. P., Schwartz, B. L., and Schacter, D. L. (2003). Feeling-of-knowing in episodic memory: an event-related fMRI study. *Neuroimage* 18, 827–836. doi:10.1016/S1053-8119(03)00014-4

Martins, S., Guillery-Girard, B., Jambaqué, I., Dulac, O., and Eustache, F. (2006). How children suffering severe amnesic syndrome acquire new concepts? *Neuropsychologia* 44, 2792–2805. doi:10.1016/j.neuropsychologia.2006.05.022

Mayes, A. R. (1999). "Amnesic syndrome," in *The Blackwell Dictionary of Neuropsychology*, eds G. J. Beaumont, P. M. Kenealy, and M. J. C. Rogers (Oxford: Blackwell Publishers Ltd), 60–64.

Meyer-Lindenberg, A., Mervis, C. B., Sarpal, D., Koch, P., Steele, S., Kohn, P., et al. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *J. Clin. Invest.* 115, 1888–1895. doi:10.1172/JCI24892

Milan, M. J. (2013). An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. *Neuropharmacology* 68, 2–82. doi:10.1016/j.neuropharm.2012.11.015

Molesworth, C. J., Bowler, D. M., and Hampton, J. A. (2005). The prototype effect in recognition memory: intact in autism? *J. Child Psychol. Psychiatry* 46, 661–672.

Montaldi, D., and Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus* 20, 1291–1314. doi:10.1002/hipo.20853

Moulin, C. J., Souchay, C., and Morris, R. G. (2013). The cognitive neuropsychology of recollection. *Cortex* 49, 1445–1451. doi:10.1016/j.cortex.2013.04.006

Nelson, T. O., and Dunlosky, J. (1991). When people's judgments of learning (JOLs) are extremely accurate at predicting subsequent recall: the "delayed-JOL effect". *Psychol. Sci.* 2, 267–270. doi:10.1111/j.1467-9280.1991.tb00147.x

Nelson, T. O., and Leonesio, R. J. (1988). Allocation of self-paced study time and the "labor-in-vain" effect. *J. Exp. Psychol. Learn. Mem. Cogn.* 14, 476–486.

Nelson, T. O., and Narens, L. (1990). "Metamemory: a theoretical framework and new findings," in *The Psychology of Learning and Motivation, Advances in Research and Theory*, ed. G. Bower (San Diego, CA: Academic Press), 125–173.

Newcombe, N. S., Lloyd, M. E., and Ratliff, K. R. (2007). "Development of episodic and autobiographical memory: a cognitive neuroscience perspective," in *Advances in Child Development and Behavior*, Vol. 35, ed. R. V. Kail (San Diego, CA: Elsevier), 37–85.

Ofen, N. (2012). The development of neural correlates for memory formation. *Neurosci. Biobehav. Rev.* 36, 1708–1717. doi:10.1016/j.neubiorev.2012.02.016

Ofen, N., Chai, X. J., Schuil, K. D. I., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2012). The development of brain systems associated with successful memory retrieval of scenes. *J. Neurosci.* 32, 10012–10020. doi:10.1523/JNEUROSCI.1082-11.2012

Ofen, N., Kao, Y.-C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2007). Development of the declarative memory system in the human brain. *Nat. Neurosci.* 10, 1198–1205. doi:10.1038/nn1950

O'Shea, A. G., Fein, D. A., Cillessen, A. H., Klin, A., and Schultz, R. T. (2005). Source memory in children with autism spectrum disorders. *Dev. Neuropsychol.* 27, 337–360. doi:10.1207/s15326942dn2703_3

Ostby, Y., Tamnes, C. K., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., and Walhovd, K. B. (2009). Heterogeneity in subcortical brain development: a structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *J. Neurosci. Off. J. Soc. Neurosci.* 29, 11772–11782. doi:10.1523/JNEUROSCI.1242-09.2009

Ostergaard, A. L. (1987). Episodic, semantic and procedural memory in a case of amnesia at an early age. *Neuropsychologia* 25, 341–357. doi:10.1016/0028-3932(87)90023-6

Palmer, S. L., Reddick, W. E., and Gajjar, A. (2007). Understanding the cognitive impact on children who are treated for medulloblastoma. *J. Pediatr. Psychol.* 32, 1040–1049. doi:10.1093/jpepsy/jsl056

Pauly-Takacs, K. (2012). *Learning and Episodic Memory Following Childhood Brain Tumour: A Case Study*. Ph.D. thesis, University of Leeds, Leeds.

Pauly-Takacs, K., Moulin, C. J. A., and Estlin, E. J. (2011). SenseCam as a rehabilitation tool in a child with anterograde amnesia. *Memory* 19, 705–712. doi:10.1080/09658211.2010.494046

Pauly-Takacs, K., Moulin, C. J. A., and Estlin, E. J. (2012). Benefits and limitations of errorless learning after surviving pediatric brain tumors: a case-study. *J. Clin. Exp. Neuropsychol.* 34, 654–666. doi:10.1080/13803395.2012.667791

Paz-Alonso, P. M., Bunge, S. A., Anderson, M. C., and Ghetti, S. (2013). Strength of coupling within a mnemonic control network differentiates those who can and cannot suppress memory retrieval. *J. Neurosci.* 33, 5017–5026. doi:10.1523/JNEUROSCI.3459-12.2013

Paz-Alonso, P. M., Ghetti, S., Donohue, S. E., Goodman, G. S., and Bunge, S. A. (2008). Neurodevelopmental correlates of true and false recognition. *Cereb. Cortex* 1991, 2208–2216. doi:10.1093/cercor/bhm246

Perner, J., and Ruffman, T. (1995). Episodic memory an autonoetic consciousness: developmental evidence and a theory of childhood amnesia. *J. Exp. Child Psychol.* 59, 516–548. doi:10.1006/jecp.1995.1024

Pfeifer, J. H., and Peake, S. J. (2012). Self-development: integrating cognitive, socioemotional, and neuroimaging perspectives. *Dev. Cogn. Neurosci.* 2, 55–69. doi:10.1016/j.dcn.2011.07.012

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., and Piolino, P. (2012). How do the different components of episodic memory develop? Role of executive functions and feature-binding abilities. *Child Dev.* 83, 1037–1050. doi:10.1111/j.1467-8624.2012.01736.x

Picard, L., Mayor-Dubois, C., Maeder, P., Kalenzaga, S., Abram, M., Duval, C., et al. (2013). Functional independence within the self-memory system: new insights from two cases of developmental amnesia. *Cortex* 49, 1463–1481. doi:10.1016/j.cortex.2012.10.003

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329. doi:10.1016/j.neuropsychologia.2009.01.020

Pirogovsky, E., Gilbert, P. E., and Murphy, C. (2006). Source and item memory for odors in children and young adults. *Dev. Neuropsychol.* 30, 739–752. doi:10.1207/s15326942dn3002_5

Rhodes, S. M., Murphy, D., and Hancock, P. J. (2011). Developmental changes in the engagement of episodic retrieval processes and their relationship with working memory during the period of middle childhood. *Br. J. Dev. Psychol.* 29, 865–882. doi:10.1111/j.2044-835X.2010.02014.x

Rhodes, S. M., Riby, D. M., Park, J., Fraser, E., and Campbell, L. E. (2010). Executive neuropsychological functioning in individuals with Williams syndrome. *Neuropsychologia* 48, 1216–1226. doi:10.1016/j.neuropsychologia.2009.12.021

Riggins, T., Rollins, L., and Graham, M. (2013). Electrophysiological investigation of source memory in early childhood. *Dev. Neuropsychol.* 38, 180–196. doi:10.1080/87565641.2012.762001

Robinson, S. J., and Temple, C. M. (2010). Atypical semantic knowledge and autobiographical memory disorder in a young adult with Downs syndrome. *Neurocase* 16, 377–396. doi:10.1080/13554791003620280

Rosenbaum, R. S., Carson, N., Abraham, N., Bowles, B., Kwan, D., Köhler, S., et al. (2011). Impaired event memory and recollection in a case of developmental amnesia. *Neurocase* 17, 394–409. doi:10.1080/13554794.2010.532138

Rouse, H., Donnelly, N., and Hadwin, J. (2004). Do children with autism perceive second-order relational features? The case of the Thatcher illusion. *J. Child Psychol. Psychiatry* 45, 1246–1257. doi:10.1111/j.1469-7610.2004.00317.x

Sacher, M., Taconnat, L., Souchay, C., and Isingrini, M. (2009). Divided attention at encoding: effect on feeling-of-knowing. *Conscious. Cogn.* 18, 754–761. doi:10.1016/j.concog.2009.04.001

Sahakian, B. J., and Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J. R. Soc. Med.* 85, 399–402.

Salmond, C. H., Ashburner, J., Connelly, A., Friston, K. J., Gadian, D. G., and Vargha-Khadem, F. (2005). The role of the medial temporal lobe in autistic spectrum disorders. *Eur. J. Neurosci.* 22, 764–772. doi:10.1111/j.1460-9568.2005.04217.x

Saran, F. (2002). Recent advances in paediatric neuro-oncology. *Curr. Opin. Neurol.* 15, 671–677. doi:10.1097/00019052-200212000-00003

Scarf, D., Gross, J., Colombo, M., and Hayne, H. (2013). To have and to hold: episodic memory in 3- and 4-year-old children. *Dev. Psychobiol.* 55, 125–132. doi:10.1002/dev.21004

Schacter, D. L. (1983). Feeling-of-knowing in episodic memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 9, 39–54.

Schmidt-Sidor, B., Wisniewski, K. E., Shepard, T. H., and Sersen, E. A. (1990). Brain growth in Down syndrome subjects 15 to 22 weeks of gestational age and birth to 60 months. *Clin. Neuropathol.* 9, 181–190.

Schneider, W., and Lockl, K. (2002). "The development of metacognitive knowledge in children and adolescents," in *Applied Metacognition*, eds T. J. Perfect and B. L. Schwartz (Cambridge: Cambridge University Press), 224–257.

Schneider, W., Vise, M., Locld, K., and Nelson, T. (2000). Developmental trends in children's memory monitoring: evidence from a judgment-of-learning task. *Cogn. Dev.* 15, 115–134. doi:10.1016/S0885-2014(00)00024-1

Schnider, A., and Ptak, R. (1999). Spontaneous confabulators fail to suppress currently irrelevant memory traces. *Nat. Neurosci.* 2, 677–681. doi:10.1038/10236

Schnyer, D. M., Nicholls, L., and Verfaellie, M. (2005). The role of VMPC in metamemorial judgments of content retrievability. *J. Cogn. Neurosci.* 17, 832–846. doi:10.1162/0898929053747694

Sherman, S. L., Allen, E. G., Bean, L. H., and Freeman, S. B. (2007). Epidemiology of Down syndrome. *Ment. Retard. Dev. Disabil. Res. Rev.* 13, 221–227. doi:10.1002/mrdd.20157

Shimamura, A. P. (2011). Episodic retrieval and the cortical binding of relational activity. *Cogn. Affect. Behav. Neurosci.* 11, 277–291. doi:10.3758/s13415-011-0031-4

Sluzenski, J., Newcombe, N., and Kovacs, S. L. (2006). Binding, relational memory, and recall of naturalistic events: a developmental perspective. *J. Exp. Psychol. Learn. Mem. Cogn.* 32, 89–100. doi:10.1037/0278-7393.32.1.89

Sobin, C., Daniels, S., Kliey-Brabeck, K., Blundell, M., Anyane-Yeboa, K., and Karayiorgou, M. (2005). Neuropsychological characteristics of children with the 22q11 deletion syndrome: a descriptive analysis. *Child Neuropsychol* 11, 39–53. doi:10.1080/09297040590911167

Sobin, C., Kiley-Brabeck, K., Daniels, S., Khuri, J., Taylor, L., Blundell, M., et al. (2004). Networks of attention in children with the 22q11 deletion syndrome. *Dev. Neuropsychol.* 26, 611–626. doi:10.1207/s15326942dn2602_5

Souchay, C., Bacon, E., and Danion, J.-M. (2006). Metamemory in schizophrenia: an exploration of the feeling-of-knowing state. *J. Clin. Exp. Neuropsychol.* 28, 828–840. doi:10.1080/13803390591000846

Souchay, C., Isingrini, M., and Espagnet, L. (2000). Relations between feeling-of-knowing and frontal lobe functioning in older adults. *Neuropsychology* 14, 299–309. doi:10.1037/0894-4105.14.2.299

Souchay, C., Moulin, C. J. A., Clarys, D., Taconnat, L., and Isingrini, M. (2007). Diminished episodic memory awareness in older adults: evidence from feeling of knowing and recollection. *Conscious. Cogn.* 16, 769–784. doi:10.1016/j.concog.2006.11.002

Souchay, C., Wojcik, D. Z., Williams, H. L., Crathern, S., and Clarke, P. (2013). Recollection in adolescents with autism spectrum disorder. *Cortex* 49, 1598–1609. doi:10.1016/j.cortex.2012.07.011

Svoboda, E., Richards, B., Polsinelli, A., and Guger, S. (2010). A theory-driven training programme in the use of emerging commercial technology: application to an adolescent with severe memory impairment. *Neuropsychol. Rehabil.* 20, 562–586. doi:10.1080/09602011003669918

Synofzik, M., Vosgerau, G., and Newen, A. (2008). I move, therefore I am: a new theoretical framework to investigate agency and ownership. *Conscious. Cogn.* 17, 411–424. doi:10.1016/j.concog.2008.03.008

Tanweer, T., Rathbone, C. J., and Souchay, C. (2010). Autobiographical memory, autonoetic consciousness, and identity in Asperger syndrome. *Neuropsychologia* 48, 900–908. doi:10.1016/j.neuropsychologia.2009.11.007

Tong, K. A., Ashwall, S., Holshouser, B. A., Nickerson, J. P., Wall, C. J., Shutter, L. A., et al. (2004). Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. *Ann. Neurol.* 56, 36–50. doi:10.1002/ana.20123

Tulving, E. (1985). How many memory systems are there? *Am. Psychol.* 40, 385–398. doi:10.1037/0003-066X.40.4.385

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Turriziani, P., Serra, L., Fadda, L., Caltagirone, C., and Carlesimo, G. A. (2008). Recollection and familiarity in hippocampal amnesia. *Hippocampus* 18, 469–480. doi:10.1002/hipo.20412

van den Bos, M., Cunningham, S. J., Conway, M. A., and Turk, D. J. (2010). Mine to remember: the impact of ownership on recollective experience. *Q. J. Exp. Psychol.* 63, 1065–1071. doi:10.1080/17470211003770938

Vargha-Khadem, F., Gadian, D. G., and Mishkin, M. (2001). Dissociations in cognitive memory: the syndrome of developmental amnesia. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1435–1440. doi:10.1098/rstb.2001.0951

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277, 376–380. doi:10.1126/science.277.5324.376

Vicari, S. (2001). Implicit versus explicit memory function in children with Down and Williams syndrome. *Downs Syndr. Res. Pract.* 7, 35–40. doi:10.3104/reports.112

Vicari, S., Belluci, S., and Carlesimo, G. A. (2003). Visual and spatial working memory dissociations: evidence from Williams syndrome. *Dev. Med. Child Neurol.* 45, 269–273. doi:10.1111/j.1469-8749.2003.tb00342.x

Vicari, S., Brizzolara, D., Carlesimo, G. A., Pezzini, G., and Volterra, V. (1996). Memory abilities in children with Williams syndrome. *Cortex* 32, 503–514. doi:10.1016/S0010-9452(96)80007-4

Vicari, S., Menghini, D., Di Paola, M., Serra, L., Donfrancesco, A., Fidani, P., et al. (2007). Acquired amnesia in childhood: a single case study. *Neuropsychologia* 45, 704–715. doi:10.1016/j.neuropsychologia.2006.08.004

von der Linden, N., and Roebers, C. M. (2006). Development changes in uncertainty monitoring during an event recall task. *Metacogn. Learn.* 1, 213–228. doi:10.1007/s11409-006-9001-6

Wellman, H. (1977). Tip of the tongue and feeling of knowing experiences: a developmental study of memory monitoring. *Child Dev.* 48, 13–21. doi:10.2307/1128875

Wilkinson, D. A., Best, C. A., Minshew, N. J., and Strauss, M. S. (2010). Memory awareness for faces in individuals with autism. *J. Autism Dev. Disord.* 40, 1371–1377. doi:10.1007/s10803-010-0995-x

Wojcik, D. Z., Allen, R. J., Brown, C., and Souchay, C. (2011). Memory for actions in autism spectrum disorder. *Memory* 19, 549–558. doi:10.1080/09658211.2011.590506

Wojcik, D. Z., Moulin, C. J., and Souchay, C. (2013a). Metamemory in children with autism: exploring "feeling-of-knowing" in episodic and semantic memory. *Neuropsychology* 27, 19–27. doi:10.1037/a0030526

Wojcik, D. Z., Waterman, A., Lestie, C., Moulin, C. J. A., and Souchay, C. (2013b). Metacognitive judgments-of-learning in adolescents with autism spectrum disorder. *Autism*. doi:10.1177/1362361313479453

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517. doi:10.1006/jmla.2002.2864

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The emergence of primary anoetic consciousness in episodic memory

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Based on an interdisciplinary perspective, we discuss how primary-process, anoetic forms of consciousness emerge into higher forms of awareness such as knowledge-based episodic knowing and self-aware forms of higher-order consciousness like autonoetic awareness. Anoetic consciousness is defined as the rudimentary state of affective, homeostatic, and sensory-perceptual mental experiences. It can be considered as the autonomic flow of primary-process phenomenal experiences that reflects a fundamental form of first-person "self-experience," a vastly underestimated primary form of phenomenal consciousness. We argue that this anoetic form of evolutionarily refined consciousness constitutes a critical antecedent that is foundational for all forms of knowledge acquisition via learning and memory, giving rise to a knowledge-based, or noetic, consciousness as well as higher forms of "awareness" or "knowing consciousness" that permits "time-travel" in the brain-mind. We summarize the conceptual advantages of such a multi-tiered neuroevolutionary approach to psychological issues, namely from genetically controlled primary (affective) and secondary (learning and memory), to higher tertiary (developmentally emergent) brain-mind processes, along with suggestions about how affective experiences become more cognitive and object-oriented, allowing the developmental creation of more subtle higher mental processes such as episodic memory which allows the possibility of autonoetic consciousness, namely looking forward and backward at one's life and its possibilities within the "mind's eye."

Keywords: episodic memory, anoetic consciousness, noetic consciousness, autonoetic consciousness, self, identity

FROM UNKNOWING TO KNOWING LEVELS OF CONSCIOUSNESS

Our evolutionary theoretical approach of understanding consciousness focuses on how lower levels of primary-process affective experience or "anoetic" consciousness emerge gradually by learning and memory into autonoetic consciousness through a progressive developmental maturation of the brain and mind (Panksepp, 1998a, 2005, 2007, 2008; Tulving, 2004, 2005; Vandekerckhove, 2009; Vandekerckhove and Panksepp, 2009, 2011). Anoetic consciousness reflects a primal state of autonomic-phenomenal awakeness, with direct experiences of oneself and the world – namely, an unknowing or "anoetic" (without explicit knowledge) consciousness consisting of perceptual, motoric-procedural and various primal emotional, homeostatic, and sensory affective states (Panksepp, 1998a; Merker, 2007). These brain-body states are all heavily dependent on subcortical neural networks, thalamic sensory relay nuclei, basal ganglia, and especially midline mesencephalic and diencephalic attentional and affective systems, which permit other neural circuits to evolve developmentally toward knowing about the world. "Knowing about the world" consists of "noetic" consciousness, based on semantic memory, relying on brain intermediate regions such as basal ganglia (amygdala, nucleus accumbens, etc.), the dorsal medial prefrontal cortex, temporal lobes, and "autonoetic consciousness," which is supported by high-order neocortical areas (especially parietal, prefrontal, and temporal) and is mediated by self-reflective mental states within time and environmental contexts. These "knowing states of consciousness" allow for higher mental activities, especially experiential "time-travel" consisting of the re-experience of past events in the service of future plans (Vandekerckhove and Panksepp, 2011). For instance, prefrontal and temporal activations are involved in the elaboration of higher ideographic cognitive semantic and episodic representations relying on anoetic consciousness related to diverse higher-order affective self-experiences supported by limbic structures as the amygdala, insula, and anterior cingulate cortex, along with increasingly complex implicit procedural representations that involve the motor cortex.

Each higher state of consciousness depends ultimately, not only on individual lived experiences, but on those extensive primary-process, evolutionarily provided networks of universal bodily existence, through various synchronizing and desynchronizing patterns of firings of diverse neural networks that are gradually beginning to be understood. In other words, that which came first in brain-mind evolution sustains a foundational influence on all higher forms of cognitive consciousness that we cherish. This integrative multilevel view helps us understand how an enormous number of conscious experiences emerge from the continuous multi-tiered flows of affective dynamics that we experience in our

daily life. Anoetic affective consciousness emerges from inherited functions of the brain, where various positive affective feelings reflect survival trajectories, while various negative affective feelings anticipate potential pathways of destruction (Panksepp and Biven, 2012).

Through the unconscious mechanisms of learning and memory, these affects are connected to environmental events in order to promote more sophisticated anticipatory behaviors through learning, and with gradual culture-promoted integration, into higher cognitive-processes that allow for internal evaluative reflections related to recall of past memories and "mind-travel" or "autonoesis." These layered levels of consciousness are hierarchically structured whereby the higher levels of consciousness are more recently emergent states of the brain, which certainly are phylogenetically more recent and develop later in infancy (Vandekerckhove, 2009; Vandekerckhove and Panksepp, 2009).

Crucial here, in the transition from anoetic to autonoetic consciousness are the variety of fine-grained neuronal associative processes of the basal ganglia and limbic system, integrating an implicit level of unconscious neural processing that allows for learning and memory. In other words, we do not experience the brain mechanisms of learning and memory, only their results. This underlying form of primary-process form of anoetic affective consciousness which is instantiated in diverse forms of qualia, including primal affective feelings, has often been neglected in consciousness studies (Panksepp, 1998a, 2007; Merker, 2007; Vandekerckhove, 2009; Solms and Panksepp, 2012). Such primal foundational processes have often been deemed to be deeply unconscious or "unexperienced," but this is not the case for the unconditional positive and negative feelings that arise from this level of neural processing (Panksepp, 1998a, 2005, 2007, 2008). Anoetic consciousness is constituted from "here and now" pre-reflective phenomenal experiences, not requiring higher-order forms of self-reflective consciousness subsumed by the concept of "awareness" (Solms and Panksepp, 2012). At the empirical level, evidence for this is provided by the fact that wherever in subcortical regions of the brain we can activate coherent emotional behaviors with electrical deep brain stimulation (DBS), those induced internal states are routinely "rewarding" and "punishing" in animal models (Panksepp, 1982, 1998a, 2005; Panksepp and Biven, 2012), corresponding perhaps to distinct human emotional feelings, since humans commonly report categorically distinct affective shifts when DBS is applied to such brain systems (see Panksepp, 1982). Our goal here is to provide a conceptual narrative that captures the flow of such primal brain processes that are comparatively hard to analyze explicitly with routine neuroscientific procedures in humans.

TRANSITIONS FROM "UNKNOWING" TO "KNOWING" FORMS OF CONSCIOUSNESS

From our perspective, a critical distinction becomes evident: from a rudimentary state of autonomic awakeness or "unknowing consciousness" reflecting primal biologically adaptive functions, brains states first become experienced at anoetic (unknowing) levels (e.g., bodily felt affective states), from which capacities for higher forms of consciousness gradually emerged with brain-mind encephalization. First, the primal experiential levels, provided "reinforcement" mechanisms for accruing knowledge about the world (noetic states, reflecting facts about the world). Further brain encephalization, led to awareness, a higher-order "knowing" form of consciousness based on semantic and episodic memory systems, which is encapsulated by Endel Tulving's concept of "autonoetic" consciousness, that provides access to higher meaning-making processes, reflected best in the arts, literature, and other cultural processes, that remain poorly understood at the neural level (Velmans, 1999, 2009; Block, 2005, 2007).[1]

IMPLICIT ANOETIC CONSCIOUSNESS

The Jamesian (James, 1890) fringe of consciousness – the stream of consciousness that is so hard to describe and study has been a mainstay of affective neuroscience (James, 1890; Panksepp, 1982, 1998a, 2005, 2008) a "missing piece" that can be integrated with our emerging understanding of higher forms of consciousness (Tulving, 2004, 2005; Vandekerckhove, 2009; Vandekerckhove and Panksepp, 2009, 2011). The "anoetic" nature of implicit primal anoetic consciousness consists of a continuous underlying stream of affective and multisensorial and procedural representations in an embodied or bodily format such as an autonomic sensation that are experienced at an unreflective level. It guides associative learning processes which then gets associated with "object-relations" in the world, and thereby become ever explicit (Goldman and Vignemont, 2009; Gallese and Sinigaglia, 2011). Such learning processes yield explicit representations over which one does not exert direct volitional control until enough higher-order brain matter (i.e., neocortex) evolved to allow the rudiments of autonoetic consciousness which in humans seems to be largely verbally mediated, but which we believe also be represented as visual and perhaps other images in pre-linguistic organisms. Thus, on an implicit level, anoetic consciousness is continuously influencing mood and behavior, thereby permitting affective and perceptual experiences to gradually have noetic properties. In other words, as a continuous state of experiencing of brain and bodily affective states as associated with external perceptual information processing, anoetic affects come to be associated with world events.

The transformation of noetic experience into awareness and autonoetic possibilities, needs further amplification of here-and-now anoetic and noetic evaluative states of mind by recursive brain-mind neural systems especially by fronto-parietal networks (Dehaene et al., 2006; Dehaene and Changeux, 2011). Only if the

[1]There are some resemblances here to Ned Blocks, "phenomenal," and "access" consciousness, which has been discussed neuroscientifically with respect to the neural correlates of consciousness (Block, 2005). However, his view does not conceptualize affective states and their role in learning, nor provide a way to conceptualize how higher forms of consciousness emerge from the lower anoetic and noetic levels that we think are essential for conceptualizing the hierarchical evolutionary strata of the brain-mind. Anoetic consciousness can be differentiated from Block's (1998, 2005) definition of "phenomenal consciousness," namely what it is like to be in a first order phenomenal state, encompassing all first-person conscious experiences, seemingly at both anoetic and noetic levels of experiencing, but need to be overtly reportable (hence a human phenomenon), while for us anoetic consciousness, by its very nature, is considered to reflect rudimentary implicit affective and perceptual brain states that are valenced, and can be possible studied in animal models because one can evaluate the affective properties of brain states as with DBS procedures. Related feelings are never unexperienced in humans, and DBS research provides experimental access to such shared feeling processes.

experience gets intense enough and therefore salient, one is able to describe, and/or reflect on it (Vandekerckhove and Panksepp, 2011). The underlying autonomic and organic state processes, arising from viscerally enriched subcortical circuits extend from the mesencephalic central gray regions, through medial diencephalic regions, toward cingulate and orbitomedial frontal cortices (Panksepp, 2007) are continuously contributing to the flow and fluctuations of anoetic consciousness that provides a critical foundation and background for higher cognitive activities.

Anoetic and noetic forms of consciousness bridge the genetically provided potentials for brain-mind states with explicit experiential contents to engender higher forms of consciousness that are rich in explicit conscious awareness (i.e., knowing what one is experiencing). This progression reflects how primal phenomenal experiences can be integrated through unconscious learning and memory processes toward an ideational enrichment of higher mental life. Thereby, a variety of changes in experiences, thoughts, and actions might be attributable to past events, including priming effects, unconscious saving effects in relearning, as well as certain forms of proactive and retroactive interferences (Kihlstrom et al., 2007). Within this continuum and from the perspective of noetic consciousness, anoetic neural substrates of consciousness may come to contain many implicit stored experiences, such as early childhood experiences. They no longer come into explicit awareness at later stages of development but which, because of various affective priming processes, may still arouse affective qualia that influence higher awareness processes. For instance, anoetic experiential feelings may be triggered by perceptually related associated situations or memories and may influence behavior in daily life (Squire and Zola-Morgan, 1991), while not being recognized by the individuals themselves.

Even if is not well recognized how behaviors are accompanied by and caused by apparently free-floating affective anoetic states, something that may be inherent to such implicitly triggered anoetic states is the possibility that what may be cognitively unconscious need not be affectively unexperienced or visually unseen at a primary-process level. Indeed, many priming paradigms have shown that cueing information can still be implicitly perceived even when there is no awareness of perceiving it, and this information can be causally efficacious in enhancing target identification when attention is oriented to the location of the correct cueing stimuli (Merickle et al., 2001). Similarly, unconscious affective information such as emotional words presented at the visually undetectable levels, can reliably modify mood states (Shevrin et al., 2012). Likewise, work with neonatally decorticated animals, along with work with congenitally anencephalic children (Merker, 2007), demonstrate that one can have primary affective, sensory, and perceptual here-and-now implicit experiences with very minimal capacity to project and transform them into higher mental processes or awareness (Panksepp, 1998a, 2005; Shewmon et al., 1999). A hemi-neglect patient who suffered a lesion in the right parietal cortex will find it difficult or impossible to shift attention to the left side or to be explicitly sensitive to anything on the left side (Driver and Vuilleumier, 2001). In such hemi-neglect, there is preservation of initial sensory pathways, in line with many other studies which have shown that considerable residual processing can still take place for neglected or extinguished stimuli without reaching the patient's awareness. Like many forms of implicit processing, this residual processing can modulate what enters into patient's awareness. These examples also illustrate that the higher cognitive regions of the brain are not essential for the generation of anoetic consciousness. However, with the maturation of the neocortex to sustain higher mental processes, those superordinate abilities probably have an intrinsic capacity to modulate lower brain-mind processes, which may be the source of the Freudian dynamic unconscious (among the more cephalized animals), which can only be scientifically well studied in humans.

ANOETIC CONSCIOUSNESS AND THE ORIGINS OF "EMBODIED AWARE STATES"

Being a "primal" embodied mental state, anoetic consciousness involves the capacity to experience body and world with sensory-perceptual immediacy and affective qualities that may emerge into higher-order awareness. It is the general representational contents of the anoetic and noetic states that determine the phenomenal character of autonoetic awareness (Churchland, 2005). The flow of these anoetic experiences does not dominate in awareness. It has no explicit object as most full-blown emotional states have (e.g., I am angry because. . .). In contrast, awareness involves focused attention to something specific inside or outside the organism in the world. Conscious awareness – the experience that one is experiencing – adds a new reflective dimension to consciousness (Dehaene and Changeux, 2011). Aware experience reflects the experience of something both perceptual and experientially contextualized along with an internal higher recognition of ownership of the experience. Processes of integration and differentiation play a crucial role in the process of emergence of conscious awareness achieved in short time periods, even of hundreds of millisecond (Edelman, 1993, 2003; Tononi and Edelman, 1998; Crick and Koch, 2003). These representations are the result of an underlying anoetic processing that lead to the construction of specific knowledge, an affectively motivated reaction or a thought. Anoetic consciousness becomes apparent in explicit awareness in a propositional format only when intense enough to mandate deliberative actions. Awareness is facilitated when attention is directed toward those external sensations and internal experiences that would otherwise not be perceived. In daily life, the experience of anoetic consciousness in normal subjects is less intense and more in the background of these subtle experiences, for instance feelings of familiarity in social situations. This may reflect inhibition/regulation that higher cortical ventromedial processes can impose on subcortical processes. Even if one does not talk about it, anoetic consciousness still may be expressed in body posture, gestures, and tone of speech. In the meanwhile, it is characterized by fluctuations of affective-somatosensorial background intensity as anoetic qualia are generated (Frijda et al., 1991). Such background psycho-physiological process entails continuous primary evaluations that gradually influence the affective ways in which one relates to the world, which in itself is quite distinct from various cognitive evaluations. These affective feelings (e.g., incipient desires and fears) and homeostatic ones (e.g., hunger and thirst) exist in order to help shape preferences intrinsically so as to anticipate the potential positive and negative consequences of actions.

The individual may choose to do various things as underlying causes of the anoetic affective flow and associated physiological changes fluctuate (e.g., increased blood pressure, skin conductance, and heart rate). These affectively rich emotional "action tendencies" that organisms experience, facilitate not only urges to act – for instance facilitation of enthusiasm via increased brain dopamine release, but also serve as a prelude to intended actions within higher levels of consciousness (Panksepp, 2007). Associated affective arousals are endogenously further regulated by other biogenic amine transmitters such as norepinephrine and serotonin, contributing to the intensity of anoetic consciousness, that may gradually emerge into explicit awareness when raw experience is transformed into noetic consciousness that fuels autonoetic awareness. Parallel and sequential implicit internal affective and cognitive processing and re-processing enables us here, through learning and memory, to give implicit and explicit meaning to our internal experience and affective expressions within both environmental as well as social interactions in ways that can help promote cognitive thought and planning of actions.

UNDERLYING MULTIMODAL FEEDBACK

The flow of anoetic consciousness is dependent on sensory-perceptual signal integration and ongoing dynamic activity in core limbic and brain-stem value systems (Edelman, 1993, 2003). If subcortical signaling is altered it follows that the global interoceptive feeling changes and the tendency to adaptively process affective changes related to the world changes too. For instance, research on emotion imitation (Hennenlotter et al., 2009) showed that denervation of muscles necessary to the facial expression of emotion leads to changes in central circuitry of emotion. Deafferentation of frown area with botulinum-toxin diminishes left amygdalar activity and functional connectivity between amygdala and several brain-stem regions implicated in the control of automatic arousal (Hennenlotter et al., 2009). The impaired feedback and integration of negative affect-related signals results in diminished activity of affective networks that control the anoetic quality of one's background experiences. Also when related brain areas are impaired, this updating function becomes impaired which normally helps thus to maintain and continuously update affective experience and the capacity to detect and interpret higher-order affective information such as own internal state learning and memory that is largely unconscious. Integral information processing in anoetic consciousness is thus continuously instantiated by multimodal feedback and large-scale neurodynamics resulting in accompanying brain neurochemical/electrical changes that regulate information processing, through presently poorly understood "laws of affect," perhaps by conversion of silent glutamateric synapses to active ones (Panksepp and Biven, 2012).

ANOETIC SELF-CONSCIOUSNESS VERSUS SELF-CONCEPTS

By bringing phenomenal experiences into reflective consciousness – we affectively experience how we "are" which may govern how we intuitively feel how we should behave in the world. These increasingly higher-order experiences are directly related to the affective conditions that inundate the core-self, a virtual neural representation of the body, the proposed foundation of all forms of consciousness – a cross-species construct for organismic mental coherence (Panksepp, 1998b; Northoff and Panksepp, 2008). The neural instantiation of anoetic experiences of the core-self have been suggested to be related to subcortical networks in the midline of the brainstem, projecting from the periaqueductal gray to basal ganglia such as the ventral striatum, and reciprocally to medial frontal cortical regions. These brain regions, critical for consciousness, may constitute a fundamental neural substrate for the free-flow of primary-process affective states, and thereby the construction of higher-order self-representations. This primal experiences of an affective core-self, may give rise to the universal global experience of personal existence, initially unreflective (i.e., not aware of itself), but providing a foundation for higher forms of selfhood and identity through learning and increasing complexity of perceptions, cognitive appraisals, and higher-order feelings (Slaby and Stephan, 2008). We would postulate, that the anoetic self involves feelings of singularity and unity that defines a creature as a singular entity, and as a coherent human being in our species (Damasio, 2003; Prebble et al., 2013) coloring autobiographical episodic memories with affects, and determining which memories we most easily cherish and seemingly spontaneously recall and which ones we try to avoid.

Aside from the primary experience of a coherent sense of self (Damasio, 2003; Prebble et al., 2013), the higher mental representation of the self, on the other hand, reflects how memories related to critical life experiences are integrated into a higher-order affective-cognitive schema. This is supported by the ability of the brain to represent the I'ness – namely the primal viscero-somatic body – the core-self – within memory, provides for both the internally experienced and externally evident coherence of organisms (Panksepp, 1998a, 2009; Northoff and Panksepp, 2008). These primal self-structures/functions may provide a fundamental basis for learning and knowing about ourselves, since the primary-process core-of-being is densely connected with many higher association networks, like the episodic and the semantic memory system (Vandekerckhove, 2009).The higher-order semantic definition of the self or self-concept, extracted out of semantic and episodic autobiography, is the model that we typically use to explicitly organize our experiences and actions (Dennett and Westbury, 2000). However, this is granted by the intrinsic integrative circuits that already exist at brain-stem levels (Solms and Panksepp, 2012). We propose that the anoetic affective core-self-experience gives the individual a sense of self in the moment, the episodic self consisting of the unified experience of the self in the present moment together with the self as integrated with past experiences and future aspirations. It results in a diachronic self-experience, that has substantial temporal stability. It allows individuals to experience themselves as being the same person over time (Panksepp, 1998b; Panksepp and Biven, 2012). The semantic-conceptual self however, a higher-order abstraction, consists of the semantic representation of oneself over time without being permeated as richly by this affective coloring of the anoetic self.

The difference between anoetic self-experience and semantic self-concept can be illustrated by an example of an elderly woman in later stages of Alzheimer's dementia described by Klein (2013a) who kept her anoetic self-experience intact but lost her episodic self. The women experienced a variety of memory problems

typically associated with late stages of dementia (e.g., loss of personal recollections, difficulties in object naming, word finding difficulties, temporal disorientation, etc.). In contrast, interviewing revealed that she maintained a sense of herself as an entity, albeit one beset by confusion. Her anoetic self, or what Klein defines as ontological self, did not collapse as a result of her cognitive deficits and loss of access to a variety of self-relevant sources of knowledge. Rather she kept an intact subjective sense of herself as a living, experiencing entity, and behaved exactly as one would expect a conscious, subjective entity to react to the cognitive chaos engendered by the severity of the disease process that was ravaging the higher reaches of her mind (Klein, 2013b).

REFLECTIVE CONSCIOUSNESS

Reflective consciousness implies primarily the capacity to have thoughts about experiences, as well as about thoughts, awareness of awareness – or meta-awareness much of which is probably unique to humans requiring expansive neocortical tissues that permit linguistic-symbolic transformation of thoughts and remembered experiences, into autobiographical perspectives (Panksepp, 2005). Mostly, explicit object-related reflective awareness springs into the foreground when the automaticity of being is not enough to handle the world. If attention within higher brain regions intensifies, reflection starts gradually to become explicit via a stream of sensorial and perceptual representations of objects in the world and events related to them. Reflective consciousness implies an explicit cognitive relationship with anoetic experiences, namely of the one who is aware and that of which one is aware. Information that becomes processed in higher awareness is then at the focus of attention, selected from competing and cooperative information channels to become more environmentally adapted and hence, cognitively predictive (Brown and Brüne, 2012). This view can also be compared with Block's (2005) notion of "access consciousness" as it refers to the ability to manipulate information for verbal reports, planning and reasoning and crucially, for higher-order behavioral control. It thus also introduces the capacity to learn and to describe one's own internal representations at higher cognitive levels that imply increasing "awareness" reflecting linguistic abilities of an individual ending up "knowing" something about his or her own internal states (Karmiloff-Smith, 1992; Cleeremans, 2008, 2011).

EPISODIC MEMORY AND AUTONOETIC CONSCIOUSNESS

Episodic memory is a past- and future-oriented, context-embedded neurocognitive memory system that re-presents autobiographical events from one's past (Tulving, 2002, 2004, 2005). Tulving (1985, 1999, 2001) initially defined episodic remembering as cognitive, symbolic, and representable. It involves the capacity to reflect upon information about past events, one's feelings during those events, and a timeline of when those experiences occurred, together with the ability to choose an event or social interaction and to recognize whether it occurred before or after some other point of reference (Robinson, 1986). Episodic memories are explicit events of one's past, stored in a past-oriented, context-embedded, neurocognitive memory system (Tulving, 1999, 2002, 2004, 2005). Still, the consolidation and recall of these episodic memories have been immersed in and emerged from and henceforth guided by states of anoetic affective consciousness. Thereby, implicit self-relevance becomes intimately related to each individual's unique feelings, thoughts, goals, and behaviors. Autonoetic consciousness as Klein (2013b) defines it, is intrinsic to, and dependent on episodic memory – i.e., it is constituted from "episodic" memories and sustains a relational (i.e., contingent) connection to episodic memory content.

Episodic memory constitutes autonoetic consciousness, whereas autobiographical memory involves autonoetic consciousness as long as it is episodic autobiographical memory. Autobiographical memory in itself is thus not sufficient for autonoetic consciousness. Autonoetic consciousness involves the retrieval of memories within time and context in an explicit way, constituted of self-reflective mental states. As mentioned before, it also contains the direction of attention into the future or prospection, whereas autobiographical memory can only be retrograde and semantic in its nature accompanied with noetic consciousness. Episodic memory constitutes an experience of continuity in time whereby the self is connected to previous points of time related with distinct feelings of personal agency and ownership. This highest form of consciousness makes use of the projection of the self in the context of future opportunities and possibilities, within the context of retrospective memories and prospective plans. It makes recurrent targeting of the "self" as a meta-representational mechanism where higher-order representations are targeting other possible representations of oneself (Klein et al., 2004; Cleeremans, 2008, 2011).

Tulving (2005) defined episodic memory, as differing from other forms of memory, its operations requiring an extended sense of self that can engage in mental time-travel. It targets past events, and integrates future hopes and possibilities. Reflective autonoetic consciousness, informs us about self-relevant sequences of events, enhancing the differentiation of our memories into personally relevant categories. It is accompanied with the experience – that the "I" (of agency) is the cause of "my own" thoughts and actions, or "ownership" of one's experiences (Klein, 2013b). Awareness here depends thus also on having a high order representation of oneself as being in a particular state, experienced time and context, a process that is subtended by the prefrontal cortex (Lau and Rosenthal, 2011).

The semantic memory system, on the other hand, contains information that is remote from what most people envision as remembering, for it holds no sense of personal time or affective context (Gardiner, 2000; Markowitsch et al., 2003; Tulving, 2005; Vandekerckhove et al., 2005; Gregg et al., 2006), and does not require the explicit re-experiencing of past events (Klein et al., 2004). Noetic self-awareness is the awareness of one's self in semantic ways, characterized by personality traits and factual self-knowledge, whereas autonoetic self-consciousness refers to explicit self-awareness in a specific affectively tinged time-space context and continuum.

THE ANOETIC WARMTH OF REMEMBRANCE

The episodic remembrance of one's own life experiences is filled with the pervasive affective consciousness associated with specific times, places, and events. It involves a detailed sensory affective-perceptual re-experiencing of events, and this is importantly

related to anoetic consciousness. The reliving of the subjective experiences is closely linked to an affective evaluation of the significance of these past experiences for oneself and with respect to one's previous and present position in the world (Markowitsch and Staniloiu, 2012). In James's (1890) view, episodic remembering and autonoetic awareness is described as "remembrance" with "warmth and intimacy" referring, we propose, to the phenomenal, self-referential flavor of anoetic consciousness and to the remembering of past value-laden episodic events or autonoetic awareness. One can actually feel oneself as if one was in previous scenarios. Episodic memory is especially dependent on the encoding and consolidation of many differentiated cognitive aspects each with many elaborations, with the remembered anoetic, affective, and environmental contexts in which they occurred. This memory system is enriched by characteristics such as the feeling of selfhood and agency, vividness; temporality; contextuality of color, taste, and smell; affective richness; and cognitive subtlety. The richness of affective coloring and value presumably arises from a host of affective systems, coded by diverse neuropeptides, which gives valuative richness to life (Panksepp, 1998a; Solms and Panksepp, 2012). As Klein (2013b) discusses, referring to Zahavi (2005) and James (1890), episodic memory connects to the past not by logical inference like it is the case in semantic memory, but by "pre-reflective directly givenness" (e.g., Zahavi, 2005). It is a feeling that "my current mental state stands for and thus is representative of an experience in my personal past" (e.g., James, 1890). Accompanied by anoetic consciousness it reflects a sense of affective attachment to my past, reflected in this warmth and intimacy or feeling of familiarity which is part of the valuative subjective quality of the mental event. And this feeling accompanying episodic recollection is made possible by episodic memory's association with autonoetic awareness. It follows that impairment in any of these episodic crucial characteristics or components, such as self-reflection, self-agency, self-ownership, and personal temporality should produce, in varying degrees, specific circumscribed impairments in episodic recollection (Klein, 2013b). Klein (2013b) illustrates this by R.B. who suffered from a serious head injury from a car accident, a number of cognitive impairments such as retrograde and anterograde amnesia for events in close temporal proximity to the accident. R.B. was still able to remember particular incidents from his life accompanied by clear temporal, spatial, and self-referential content. However, he no longer felt ownership of the memories, warmth and intimacy, or autonoetic consciousness.

In contrast, semantic memories do not have these abundant dependencies on anoetic consciousness – neither the contextual variables nor associated self-referential dynamics that give episodic memories such personal closeness and feelings of ownership and selfhood. Semantic memory can be self-referential and spatial (Klein, 2013a) as it consists of factual knowledge about the self and world abstracted from the specific episodic contexts from which the knowledge had been acquired. This distinction between episodic and semantic memorial experiences can also be seen, as Klein (2013b) described, as one of differences in manner of acquaintance (e.g., Russell, 1916/1999). We are acquainted with semantic pastness indirectly via inference, whereas our acquaintance with episodic pastness is directly given as the phenomenological feeling that we are re-living our past (Klein, 2013b).

Severe impairment of episodic memory retrieval, particularly of the emotional information from specific autobiographical content has been found in patients with lesions that include amygdaloid complexes and related circuitry with forebrain regions (Markowitsch and Staniloiu, 2012). The amygdala's main function is to affectively charge cues, especially in aggressive, fearful, and sexual domains, so that explicit or implicit memory events of a specific anoetic significance can be successfully searched within the appropriate neural nets and thereby re-activated (Markowitsch and Staniloiu, 2012). Emotionally stressful life events impact the amygdala and the hippocampus – areas with a rich density of glucocorticoid receptors – so as to consolidate especially stressful memories. The Papez circuit and the basolateral limbic loop (mediodorsal nucleus of the thalamus, subcallosal area, amygdala, and interconnecting fiber) are also involved. The Papez and the basolateral limbic circuit represent a group of "bottleneck-structures" that are interconnected and of high relevance for the extraction of the affective, somatosensorial, and social significance of new incoming information (Markowitsch and Staniloiu, 2012). In contrast, when damage involves just the semantic memory system, especially of the hippocampus, patients may forget personal facts and beliefs – where and when they were born, details of their physical appearance, but their anoetic self remains relatively intact.

CONCLUSION AND SUMMATION: UNKNOWING ANOETIC CONSCIOUSNESS GUIDES THE EMERGENCE OF KNOWING CONSCIOUSNESS

Anoetic consciousness has here been envisioned as a stream of pre-reflective affective and sensorial perceptual consciousness essential for the waking state of the organism in the absence of an explicit self-referential awareness of associated cognitive contents. This state of affective consciousness acts as a bridge that may take us from deeply unconscious information processing and primary-process affective and perceptual consciousness toward the possibility of knowing (noetic) levels of consciousness situated within the basal ganglia that mediate learning and memory and higher regions of the brain, such as the neocortex which allows for mental time-travel from the permutations of these memories. In other words, unknowing consciousness, namely anoetic consciousness, allows various primordial affective feelings, and the related affective information processing of learning and memory mechanisms, especially in brain structures known as the basal ganglia (amygdala, nucleus accumbens, bed nuclei of the stria terminalis) to connect up with knowing noetic, and especially, autonoetic consciousness. Anoetic self-experience influences global phenomenal experiences – unconditional states of being – which not only modulate the affective tone of one's behavior, but provide critical information for learning and memory. As primarily pre-conceptual phenomena, anoetic affective experiences, can be differentiated into various intrinsic valuative processes of the brain (emotional, homeostatic, and sensory affects) that become continuously part of actual information processing and existential perception of the world. Later in development, when reflection is possible, those primal affects act as free-flowing streams

underlying the more cognitively detailed aspects of our continuously ongoing cognitive-noetic and autonoetic information processing as thoughts, images, fantasies, expectations, and anticipations. This is very similar to the "free flow of consciousness" that James (1890) talked about. In contrast to noetic consciousness, autonoetic consciousness refers to the reflective capacity to mentally represent a continuing existence one that is embedded in specific episodic contexts and associated with remembered experiences with affective quality – from "warmth and intimacy" to "dread and alienation."

Noetic consciousness is associated with the knowledge that specific facts have happened in the past, but it has no access to a fully resolved, affectively rich awareness of one's ongoing subjective experience. Noetic self-awareness is the awareness of one's self in semantic ways, characterized by personality traits and factual self-knowledge, whereas autonoetic consciousness refers to explicit self-awareness, and/or the explicit awareness of something or someone else in a specific affectively tinged time-space context. This highest episodic self-referential form of consciousness makes use of the projection of the self in the context of future opportunities and possibilities, within the context of retrospective memories and prospective plans. As a self-generative, self-knowing state, attention in autonoetic consciousness can thus be directed to memories of the past – of being retrospective, with past anoetic flows of consciousness available in the "real-time" present, and planning and dreaming of the future in a prospective form of autonoetic consciousness. It is accompanied with a sense of personal agency; that is, the belief that I am the cause of my thoughts and actions, a sense of personal ownership; that is, the feeling that my thoughts and acts belong to me, and the ability to think about time as an unfolding of personal happenings centered about the self (Klein, 2013a).

This form of mentalizing, surely most highly developed in humans, is heavily mediated by medial temporal lobe (hippocampal) and frontal lobe evolution and microstructure (Buckner and Carroll, 2007; Fleming et al., 2010). Neural correlates of noetic (knowing) consciousness relate to various memory abilities, especially declarative (factual) memory, whereas anoetic consciousness is heavily linked, to raw sensorial and perceptual abilities, to various subcortical affective processes, and intrinsic affective value structures, and hence, is more related to limbic and paralimbic structures associated intrinsically with the more implicit free-flow of affective consciousness. We suggest that what came first in the evolution of consciousness, namely the anoetic forms, sustain primacy in the construction of the higher, noetic and especially autonoetic forms that are of such critical importance for our individual decision-making abilities and autobiographical existences.

REFERENCES

Block, N. (1998). "On a confusion about a function of consciousness," in *The Nature of Consciousness: Philosophical Debates*, eds N. Block, O. Flanagan, and G. Guzeldere (Cambridge: MIT Press), 375–415.

Block, N. (2005). Two neural correlates of consciousness. *Trends Cogn. Sci. (Regul. Ed.)* 9, 46–52. doi:10.1016/j.tics.2004.12.006

Block, N. (2007). Consciousness, accessibility, and the mesh between psychology and neuroscience. *Behav. Brain Sci.* 30, 481–548. doi:10.1017/S0140525X07002786

Brown, E. C., and Brüne, M. (2012). The role of prediction in social neuroscience. *Front. Hum. Neurosci.* 6:147. doi:10.3389/fnhum.2012.00147

Buckner, R. L., and Carroll, D. C. (2007). Self-projection and the brain. *Trends Cogn. Sci.* 11, 49–57. doi:10.1016/j.tics.2006.11.004

Churchland, P. (2005). Brain wide shut. *New Sci.* 39, 46–49.

Cleeremans, A. (2008). Consciousness: the radical plasticity thesis. *Prog. Brain Res.* 168, 19–33. doi:10.1016/S0079-6123(07)68003-0

Cleeremans, A. (2011). The radical plasticity thesis: how the brain learns to be conscious. *Front. Psychol.* 2:86. doi:10.3389/fpsyg.2011.00086

Crick, F., and Koch, C. (2003). A framework for consciousness. *Nat. Neurosci.* 6, 119–126. doi:10.1038/nn0203-119

Damasio, A. (2003). Feelings of emotion and the self. *Ann. N. Y. Acad. Sci.* 1001, 253–261. doi:10.1196/annals.1279.014

Dehaene, S., and Changeux, J. P. (2011). Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227. doi:10.1016/j.neuron.2011.03.018

Dehaene, S., Changeux, J. P., Naccache, L., Sackur, J., and Sergent, C. (2006). Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends Cogn. Sci.* 10, 204–211. doi:10.1016/j.tics.2006.03.007

Dennett, D., and Westbury, C. (2000). "Mining the past to construct the future: memory and belief as forms of knowledge," in *Memory, Brain, and Belief*, eds D. L. Schacter and E. Scarry (Cambridge, MA: Harvard University Press), 11–34.

Driver, J., and Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition* 79, 39–88. doi:10.1016/S0010-0277(00)00124-4

Edelman, G. (1993). Neural Darwinism: selection and reentrant signaling in higher brain function. *Neuron* 10, 115–125. doi:10.1016/0896-6273(93)90304-A

Edelman, G. (2003). Naturalizing consciousness: a theoretical framework. *Proc. Natl. Acad. Sci. U.S.A.* 100, 5520–5524. doi:10.1073/pnas.0931349100

Fleming, S. M., Weil, R. S., Nagy, Z., Dolan, R. J., and Rees, G. (2010). Relating introspective accuracy to individual differences in brain structure. *Science* 329, 1541–1543. doi:10.1126/science.1191883

Frijda, N. H., Mesquita, B., Sonnemans, J., and Van Goozen, S. (1991). "The duration of affective phenomena or emotions, sentiments and passions," in *International Review of Studies on Emotion*, Vol. 1, ed. K. T. Strongman (New York: Wiley), 187–225.

Gallese, V., and Sinigaglia, C. (2011). What is so special about embodied simulation? *Trends Cogn. Sci.* 15, 515. doi:10.1016/j.tics.2011.09.003

Gardiner, J. M. (2000). "On the objectivity of subjective experiences of autonoetic and noetic consciousness," in *Memory, Consciousness, and the Brain: The Tallinn Conference*, ed. E. Tulving (Philadelphia: The Psychology Press), 159–172.

Goldman, A., and Vignemont, F. (2009). Is social cognition embodied? *Trends Cogn. Sci.* 13, 154–159. doi:10.1016/j.tics.2009.01.007

Gregg, V., Gardiner, J., Karayianni, I., and Konstantinou, I. (2006). Recognition memory and awareness: a high-frequency advantage in the accuracy of knowing. *Memory* 14, 265–275. doi:10.1080/09658210544000051

Hennenlotter, A., Dresel, C., Castrop, F., Baumann, A. O., Wohlschläger, A. M., Haslinger, B., et al. (2009). The link between facial feedback and neural activity within central circuitries of emotion – new insights from botulinum toxin-induced denervation of frown muscles. *Cereb. Cortex* 19, 537–542. doi:10.1093/cercor/bhn104

James, W. (1890). *The Principles of Psychology*. New York, NY: Macmillan.

Karmiloff-Smith, A. (1992). *Beyond Modularity: A Developmental Perspective on Cognitive Science*. Cambridge: MIT Press.

Kihlstrom, J. F., Dorfman, J., and Park, L. (2007). "Implicit and explicit memory and learning," in *The Blackwell Companion to Consciousness*, eds M. Velmans and S. Schneider (Malden, MA: Blackwell Publishing Ltd), 525–539.

Klein, S., German, T., Cosmides, L., and Gabriel, R. (2004). A theory of autobiographical memory: necessary components and disorders resulting from their loss. *Soc. Cogn.* 22, 460–490. doi:10.1521/soco.22.5.460.50765

Klein, S. B. (2013a). "The two selves: the self of conscious experience and its brain," in *Handbook of Self and Identity*, eds M. R. Leary and J. P. Tangney (New York: Guilford Publications), 617–637.

Klein, S. B. (2013b). Making the case that episodic recollection is attributable to operations occurring at retrieval rather than to content stored in a dedicated subsystem of long-term memory. *Front. Behav. Neurosci.* 7:3. doi:10.3389/fnbeh.2013.00003

Lau, H., and Rosenthal, D. (2011). Empirical support for higher-order theories of conscious awareness. *Trends Cogn. Sci. (Regul. Ed.)* 15, 365–373. doi:10.1016/j.tics.2011.05.009

Markowitsch, H. J., and Staniloiu, A. (2012). Amnesic disorders. *Lancet* 380, 1429–1440. doi:10.1016/S0140-6736(11)61304-4

Markowitsch, H. J., Vandekerckhove, M. M. P., Lanfermann, H., and Russ, M. O. (2003). Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. *Cortex* 39, 643–665. doi:10.1016/S0010-9452(08)70858-X

Merickle, P. M., Smilek, D., and Eastwood, J. D. (2001). Perception without awareness: perspectives from cognitive psychology. *Cognition* 79, 115–134. doi:10.1016/S0010-0277(00)00126-8

Merker, B. (2007). Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. *Behav. Brain Sci.* 30, 63–81. doi:10.1017/S0140525X07000891

Northoff, G., and Panksepp, J. (2008). The trans-species concept of self and the subcortical-cortical midline system. *Trends Cogn. Sci.* 12, 259–264. doi:10.1016/j.tics.2008.04.007

Panksepp, J. (1982). Toward a general psychobiological theory of emotions. *Behav. Brain Sci.* 5, 407–467. doi:10.1017/S0140525X00012759

Panksepp, J. (1998a). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. New York: Oxford University Press.

Panksepp, J. (1998b). The periconscious substrates of consciousness: affective states and the evolutionary origins of the self. *J. Conscious. Stud.* 5, 566–582.

Panksepp, J. (2005). Affective consciousness: core emotional feelings in animals and humans. *Conscious. Cogn.* 14, 30–80. doi:10.1016/j.concog.2004.10.004

Panksepp, J. (2007). "Affective consciousness," in *The Blackwell Companion to Consciousness*, eds M. Velmans and S. Schneider (Malden, MA: Blackwell Publishing, Ltd), 114–129.

Panksepp, J. (2008). "The affective brain and core-consciousness: how does neural activity generate emotional feelings?," in *The Handbook of Emotions*, 2nd Edn, eds M. Lewis, J. Haviland, and L. F. Barrett (New York: Guilford), 47–67.

Panksepp, J. (2009). "Core consciousness," in *The Oxford Companion to Consciousness*, eds T. Bayne, A. Cleeremans, and P. Wilken (Oxford: Oxford University Press), 198–200.

Panksepp, J., and Biven, L. (2012). *The Archaeology of Mind: Neuroevolutionary Origins of Human Emotion*. New York: W.W. Norton.

Prebble, S. C., Addis, D. R., and Tippett, L. J. (2013). Autobiographical memory and sense of self. *Psychol. Bull.* 139, 815–840. doi:10.1037/a0030146

Robinson, J. A. (1986). "Temporal reference systems and autobiographical memory," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 159–188.

Russell, B. (1916/1999). *The Problems of Philosophy*. Mineola, NY: Dover Publications.

Shevrin, H., Panksepp, J., Brakel, L. A. W., and Snodgrass, M. (2012). Subliminal affect valence words change conscious mood potency but not valence: is this evidence for unconscious valence affect? *Brain Sci.* 2, 504–522. doi:10.3390/brainsci2040504

Shewmon, D. A., Holmes, G. L., and Byrne, P. A. (1999). Consciousness in congenitally decorticated children: developmental vegetative state as self-fulfilling prophecy. *Dev. Med. Child. Neurol.* 41, 364–374. doi:10.1017/S0012162299000821

Slaby, J., and Stephan, A. (2008). Affective intentionality and self-consciousness. *Conscious. Cogn.* 17, 506–513. doi:10.1016/j.concog.2008.03.007

Solms, M., and Panksepp, J. (2012). The "Id" knows more than the "Ego" admits: neuropsychoanalytic and primal consciousness perspectives on the interface between affective ad cognitive neuroscience. *Brain Sci.* 2, 147–175. doi:10.3390/brainsci2020147

Squire, L. R., and Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science* 253, 1380–1386. doi:10.1126/science.1896849

Tononi, G., and Edelman, G. M. (1998). Consciousness and complexity. *Science* 282, 1846–1851. doi:10.1126/science.282.5395.1846

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi:10.1037/h0080017

Tulving, E. (1999). "On the uniqueness of episodic memory," in *Cognitive Neuroscience of Memory*, eds L. G. Nilsson and H. J. Markowitsch (Göttingen: Hogrefe and Huber Publishers), 11–42.

Tulving, E. (2001). "The origin of autonoesis in episodic memory," in *The Nature of Remembering: Essays in Honor of Robert G. Crowder*, eds H. L. Roediger, J. S. Nairne, I. Neath, and A. M. Suprenant (Washington, DC: American Psychological Association), 17–34.

Tulving, E. (2002). "Chronesthesia: awareness of subjective time," in *Principles of Frontal Lobe Function*, eds D. T. Stuss and R. C. Knight (New York: Oxford University Press), 311–325.

Tulving, E. (2004). Episodic memory from mind to brain. *Rev. Neurol. (Paris)* 160, 9–23. doi:10.1016/S0035-3787(04)70940-6

Tulving, E. (2005). "Episodic memory and autonoesis: uniquely human?," in *The Missing Link in Cognition: Self-Knowing Consciousness in Man and Animals*, eds H. S. Terrace and J. Metcalfe (New York: Oxford University Press), 3–56.

Vandekerckhove, M., and Panksepp, J. (2009). The flow of anoetic to noetic and autonoetic consciousness: a vision of unknowing anoetic and knowing noetic consciousness in the remembrance of things past and imagined futures. *Conscious. Cogn.* 18, 1018–1028. doi:10.1016/j.concog.2009.08.002

Vandekerckhove, M., and Panksepp, J. (2011). The neural evolution of consciousness: from anoetic affective experiences to noetic and autonoetic cognitive awareness. *Neurosci. Biobehav. Rev.* 35, 2017–2025. doi:10.1016/j.neubiorev.2011.04.001

Vandekerckhove, M. M., Markowitsch, H. J., Mertens, M., and Woermann, F. G. (2005). Bi-hemispheric engagement in the retrieval of autobiographical episodes. *Behav. Neurol.* 16, 203–210.

Vandekerckhove, M. M. P. (2009). Memory, consciousness and the self. Consciousness as a continuum of states. *Self Identity* 8, 4–23. doi:10.1080/15298860801961927

Velmans, M. (1999). When perception becomes conscious. *Br. J. Psychol.* 90, 543–566. doi:10.1348/000712699161620

Velmans, M. (2009). How to define consciousness and how not to define consciousness. *J. Conscious. Stud.* 16, 139–156.

Zahavi, D. (2005). *Subjectivity and Selfhood: Investigating the First-Person Perspective*. Cambridge, MA: MIT Press.

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Medial temporal lobe contributions to intra-item associative recognition memory in the aging brain

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Aging is associated with a decline in episodic memory function. This is accompanied by degradation of and functional changes in the medial temporal lobe (MTL) which subserves mnemonic processing. To date no study has investigated age-related functional change in MTL substructures during specific episodic memory processes such as intra-item associative memory. The aim of this study was to characterize age-related change in the neural correlates of intra-item associative memory processing. Sixteen young and 10 older subjects participated in a compound word intra-item associative memory task comprising a measure of associative recognition memory and a measure of recognition memory. There was no difference in performance between groups on the associative memory measure but each group recruited different MTL regions while performing the task. The young group recruited the left anterior hippocampus and posterior parahippocampal gyrus whereas the older participants recruited the hippocampus bilaterally. In contrast, recognition memory was significantly worse in the older subjects. The left anterior hippocampus was recruited in the young group during successful recognition memory whereas the older group recruited a more posterior region of the left hippocampus and showed a more bilateral activation of frontal brain regions than was observed in the young group. Our results suggest a reorganization of the neural correlates of intra-item associative memory in the aging brain.

Keywords: associative memory, medial temporal lobe, hippocampus, perirhinal cortex, aging

INTRODUCTION

The medial temporal lobes (MTL) contain structures that are crucial for memory processing, such as the hippocampus, perirhinal cortex, and the parahippocampal gyrus. Damage to these structures invariably results in episodic memory impairment (Scoville and Milner, 1957). A growing body of evidence indicates that substructures within the MTL support different elements of episodic memory processing. The hippocampus is implicated in between-domain associative memory (Mayes et al., 2004; Konkel et al., 2008), that is the high level integration and "binding" of perceptual and conceptual information which are processed and stored in distal brain regions with weak or no direct connectivity with each other. In contrast, extra hippocampal cortical structures such as the perirhinal cortex are implicated in intra-item associative memory (Bussey et al., 2005), that is the unitization of perceptual or conceptual domains represented in closely interacting cortical regions (Davachi, 2006; Mayes et al., 2007). Additional memory functions have also been attributed to these structures. As such, it is argued that the hippocampus is crucial for recollection based recognition memory whereas the perirhinal cortex underlies familiarity based recognition memory (Mayes et al., 2007). In addition, existing evidence shows that memory processing of verbal information or information with a semantic content is lateralized to the anterior regions of the left MTL (Parsons et al., 2006; Ford et al., 2010).

Episodic memory functions decline with age (Christensen, 2001; Nyberg et al., 2003; Ronnlund et al., 2005; Schaie, 2005; Troyer et al., 2011) and young adults consistently outperform older adults on memory tasks which are hypothesized to be hippocampal dependent (Shaw et al., 2006; Head and Isom, 2010; Harris and Wolbers, 2012). MRI and *postmortem* pathological investigations have shown that among MTL substructures, the hippocampus is particularly sensitive to age-related change (Jack et al., 1998; Raz et al., 2004; Raz and Rodrigue, 2006) with the subiculum and dentate gyrus particularly affected in non-demented older adults (West, 1993; Small et al., 2002). In contrast, the perirhinal cortex appears to undergo little age-related atrophy (Insausti et al., 1998). Functional imaging studies consistently show age-related reductions in BOLD signal in the MTL during memory task performance (Daselaar et al., 2003; St Jacques et al., 2012).

Investigations of age-related change in the neural correlates of episodic memory retrieval suggest that in parallel with reductions in MTL activation, performance in older adults is associated with the recruitment of additional brain regions, often resulting in a bilateral pattern of activation in the MTL and in frontal cortical regions (Cabeza, 2001; Maguire and Frith, 2003; Giovanello and Schacter, 2012). Whether changes in brain activation as people get older are observed regardless of the type of episodic memory processes involved remains incompletely understood. It is unknown whether age-related changes in activation within and

beyond the MTL are also found for specific types of associative memory processing such as intra-item associative memory. To address this issue, the present study aimed to: (1) compare intra-item associative recognition memory performance in young and older healthy adults, and (2) establish age-related changes in the neural correlates of intra-item associative recognition memory within the MTL. We used an associative memory task for compound words which included previously studied (targets) and novel items (foils). Some of the novel items were recombined elements of studied components.

We hypothesized that: (1) young adults would outperform older adults on a compound word intra-item associative recognition memory task, (2) successful intra-item associative recognition memory of compound words would recruit greater left > right MTL structures, and (3) the older group would show decreased hippocampal activity compared to the young group.

MATERIALS AND METHODS

PARTICIPANTS

Sixteen, young (12 females) (mean age = 26 years, range = 21–37 years) and 10 older (5 females) (mean age = 70 years, range = 62–77 years) right-handed healthy volunteers were recruited for this study. All were native English speakers with normal or corrected to normal vision and reported no significant neurological or psychiatric disorders on a medical questionnaire. All participants underwent a cognitive screening assessment using the Addenbrooke's Cognitive Examination-Revised (ACE-R). This study was approved by the University of New South Wales Human Ethics Research Committee and all participants provided written informed consent.

STIMULUS MATERIALS

This study comprised a verbal intra-item associative memory task, adapted from a previous publication (Mayes et al., 2007). Stimuli comprised 100 two- or three-syllable compound words (e.g., gateway, highchair). All stimuli were printed in black on a white background. Three different versions of the task were created and lists were randomly allocated across participants.

PROCEDURES

The entire experiment was conducted in the scanner and functional magnetic resonance imaging data were acquired during both encoding and test phases. All responses were recorded using an MR compatible button box. At encoding, 60 stimuli were presented on a Phillips LCD monitor one at a time in the center of the screen for 2000 ms, followed by a fixation point for 1000 ms. To ensure optimal attention to the stimuli at encoding, participants were instructed to indicate for each stimulus whether the word was pleasant, unpleasant, or neutral. Before the study phase participants were informed: "You will be shown a number of words. Please tell me if each word evokes a pleasant, unpleasant, or neutral feeling." Encoding was immediately followed by a test phase. At test, 60 stimuli were presented one at time using the same timing procedure. Twenty stimuli were identical to the ones seen at study ("identical"), 20 were novel stimuli not seen at study ("novel"), and 20 stimuli were the combination of two stimuli seen at study ("recombined") (e.g., *highchair* and *gateway* at encoding were recombined to become *highway* at test; **Figure 1**). Memory for the stimuli seen at study was tested using a yes/no recognition procedure. For each item, participants were instructed to indicate "yes" if they thought the stimulus had been presented at encoding, or "no" if they thought the stimulus had not been seen at encoding. Before the test phase participants were informed: "You will now be shown some more words. For each word please do the following. If you saw the word earlier, press the left button. If you did not see the word earlier, press the right button." Participants were also instructed to respond within the 2000-ms stimulus presentation window. At test, the order of presentation of identical, recombined, and novel stimuli was pseudo-randomized, in that no items from the same category were seen in succession. In order to become familiarized with the general procedure, participants took part in a practice trial of the encoding and test phases outside the scanner. Participants were not informed about the recombined items at any stage of the experiment.

MR IMAGING PROTOCOL

MR imaging was acquired on a 3-T Philips Achieva MRI scanner with standard quadrature head coil (16 channels). Functional MR images consisted of the following scanning parameters: 33 slices were collected per image volume covering the whole brain. Scanning parameters for the echo planar imaging (EPI) sequence were as follows: repetition time/echo time (TR/TE) 2000/30 ms; flip angle (FA) 80°; slice thickness 3.5 mm with a 0-mm interslice gap. For the current task (see below), two encoding runs were collected (75 acquisitions per run). Each encoding run was immediately followed by a test run (75 acquisitions per run). In addition, all participants underwent a whole brain T1 coronal orientation, matrix 256 × 256, 180 slices, 1 mm isotropic, TE/TR = 2.5/5.4 ms, FA $\alpha = 8°$.

fMRI DATA ANALYSIS

Images were analyzed using fMRI Expert Analysis Tool (FEAT) version 5.98, a part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Pre-processing of each individual's fMRI dataset included: removal of non-brain structures from the T1 structural scans using Brain Extraction Tool (BET), motion correction using MCFLIRT, non-brain structures were removed from the echoplanar imaging volumes using BET, spatial smoothing using a Gaussian Kernel of FWHM 5 mm; mean based intensity normalization of the entire 4D dataset by the same multiplicative factor; high pass temporal filtering (Gaussian weighted least-squares straight line fitting, with $\sigma = 100$ s). Time series statistical analysis was performed using FILM with local autocorrelation correction. Functional scans were registered to the high resolution T1 structural scan per participant and to the standard Montreal Neurological Institute (MNI 152) standard space template image using affine registration with FLIRT. Coordinates (x, y, z) of activation are reported in MNI space.

For each subject a fixed effects model was used to estimate effects for each stimulus type. The following contrasts were modeled: identical item hits vs. correct novel item rejections and identical item hits vs. correct recombined item rejections. The resulting data were then entered into a mixed effects higher level analysis to investigate activity across participants for each comparison.

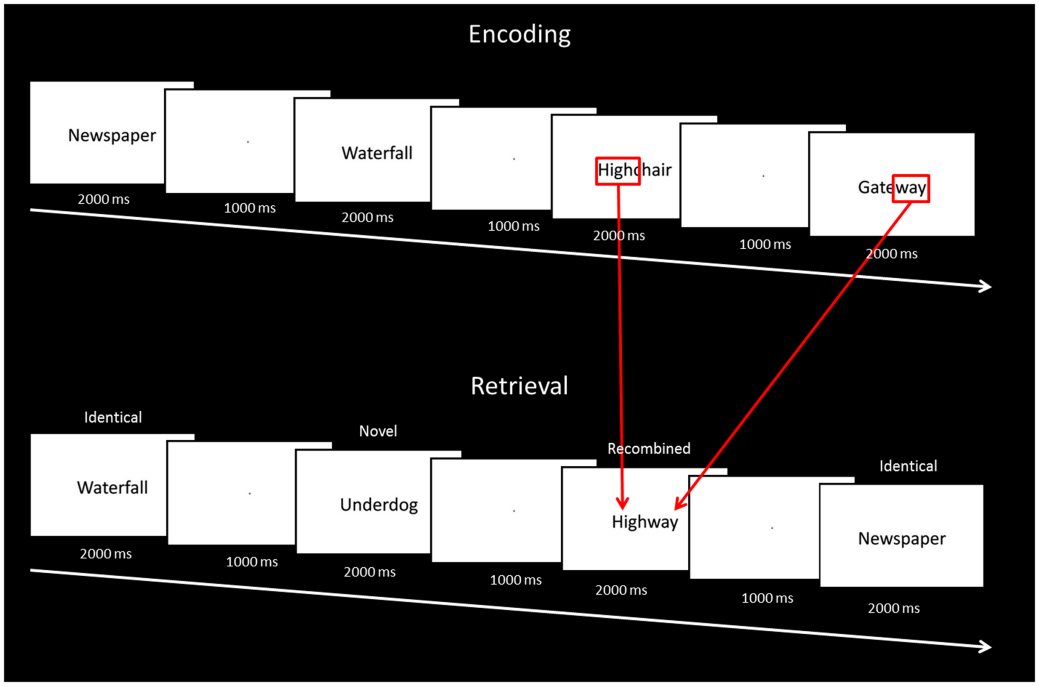


FIGURE 1 | Description of the study and test phases of the intra-item associative memory task.

Z statistic images were thresholded using clusters determined by $Z > 2.3$ and an uncorrected cluster significance threshold of $p < 0.01$. In addition, the % signal change within each cluster was extracted for each group.

RESULTS

BEHAVIORAL

Performance on the general cognitive measure ACE-R was not significantly different between the young and older groups. Corrected recognition memory for identical compound words (i.e., hits-false alarms) differed significantly between groups, with the young participants outperforming their older counterparts [85 and 58% respectively; $t(24) = 4.568$, $p = < 0.001$]. In contrast, no significant group differences were found in identifying either *recombined* [57 and 42% respectively; $t(24) = 1.630$, $p = 0.116$] or *novel* compound words [95 and 91% respectively; $t(24) = 1.182$, $p = 0.249$] (**Figure 2**). Investigating within group performance, we found significant differences in accuracy between identical and recombined items [85 vs. 57%, $t(30) = 4.951$, $p = < 0.001$], between recombined and novel items [57 vs. 95%, $t(30) = -7.535$, $p = < 0.001$], and between identical and novel items [85 and 95%, $t(30) = -3.162$, $p = 0.004$] in the young group. In contrast, in the older group, there was a significant difference in accuracy between recombined and novel items [42 and 91%, $t(18) = -5.247$, $p = < 0.001$] and identical and novel items [58 and 91%, $t(18) = -4.693$, $p = < 0.001$] but no significant difference between identical and recombined items [58 and 48%, $t(18) = 1.540$, $p = 0.141$].

Analyses on response latency revealed that in the young group, correct responses to recombined items (1160 ± 271 ms) were significantly slower than responses to identical [1003 ± 243 ms, $t(681) = -7.96$, $p = < 0.001$] and novel [1008 ± 262 ms, $t(683) = 7.43$, $p < 0.001$] items. No significant difference was found in response latency between identical and novel items. In the older group, correct responses to recombined items (1246 ± 285 ms) were significantly slower than responses to

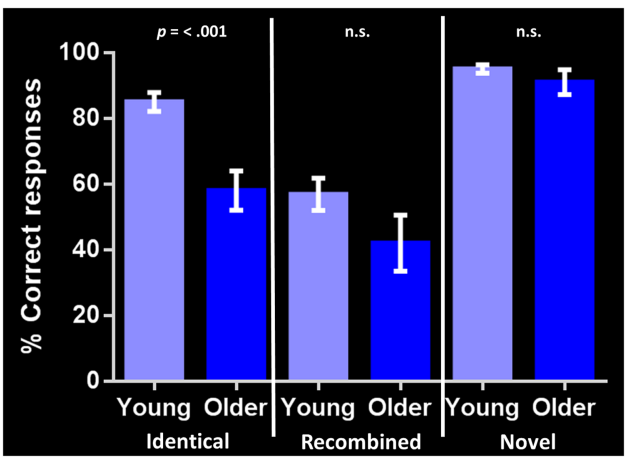


FIGURE 2 | Corrected recognition memory performance for each stimulus condition in young and older adults (i.e., hits-false alarms). The bar chart shows the percent correct response for each stimulus type (identical, recombined, novel). Error bars represent the standard error of the mean. $p = < 0.001$ indicates significant difference between young and older adult groups. n.s., indicates non-significant difference.

identical [1112 ± 280 ms, $t(332) = -4.327$, $p = < 0.001$] and novel [1084 ± 280 ms, $t(334) = 5.233$, $p = < 0.001$] items. No significant difference was found in response latency between identical and novel items.

The young group responded significantly faster than the older group for all item types: identical [young: 1003 ± 243 ms; older: 1112 ± 278 ms; $t(521) = -4.6$, $p = < 0.001$], recombined [young: 1159 ± 271 ms; older: 1246 ± 285 ms; $t(494) = -3.3$, $p = < 0.001$], and novel [young: 1008 ± 262 ms; older: 1084 ± 280 ms; $t(523) = -3.08$, $p = 0.002$]. The number of late responses (i.e., >2000 ms) did not differ between the young and older groups.

IMAGING

Associative recognition memory (identical vs. recombined contrast)

In the young group, the identical vs. recombined rejection contrast revealed significant activation within the MTL in two regions of the left hippocampus ($x = -36$, $y = -24$, $z = -14$ and $x = -26$, $y = -14$, $z = -22$) and in the left posterior parahippocampal gyrus ($x = -26$, $y = -38$, $z = -10$) (**Figure 3A**; **Table 1**). In addition, significant clusters of activation were also observed in the middle frontal gyrus, putamen, lateral occipital cortex, precentral gyrus, posterior cingulate gyrus, supramarginal gyrus, and frontal pole bilaterally (**Table 1**).

The same contrast in the older group revealed significant activation within the MTL in the hippocampus bilaterally (right: $x = 36$, $y = -18$, $z = -16$ and left: $x = -30$, $y = -20$, $z = -14$) and the left perirhinal cortex ($x = -32$, $y = -14$, $z = -32$) (**Figure 3B**; **Table 1**). Additional significant activation was observed in the insular cortex, posterior cingulate cortex, occipital fusiform gyrus, and the middle frontal gyrus (**Table 1**).

Recognition memory (identical vs. novel contrast)

In the young adult group, the identical vs. novel item contrast revealed a significant cluster of activation in the left anterior hippocampus ($x = -28$, $y = -14$, $z = -24$; **Figure 4A**; **Table 2**). In addition, significant activation in were found in the lateral occipital cortex, middle frontal gyrus, frontal pole, thalamus, superior frontal gyrus, and precuneus (**Table 2**).

In the older group, the same contrast revealed a small cluster of activation within the left hippocampus ($x = -14$, $y = -16$, $z = -22$; **Figure 4B**; **Table 2**). Broad bilateral activation was also present in the middle frontal gyrus and the frontal pole, as well as in the angular gyrus, superior frontal gyrus, lateral occipital cortex, precentral gyrus, paracingulate gyrus, and the supramarginal gyrus (**Table 2**).

DISCUSSION

This study identified the neural correlates of associative recognition memory for compound words in young and older healthy adults. Although performance in associative recognition memory was matched between groups, young and older adults differed in the location and extent of MTL involvement supporting task

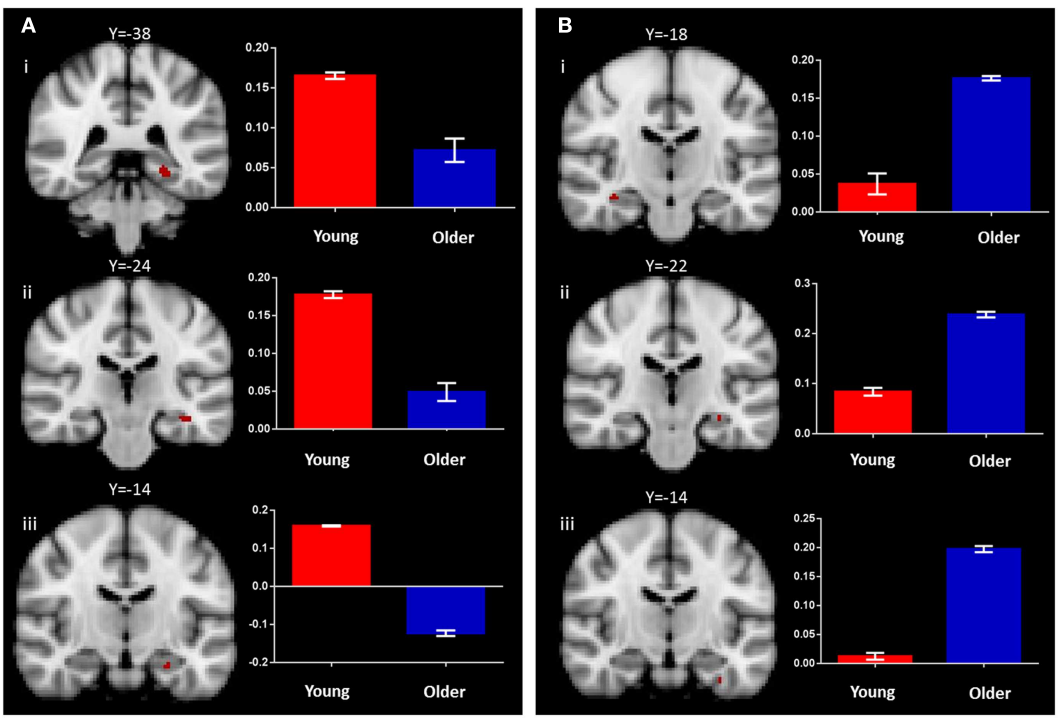


FIGURE 3 | Regions of increased BOLD signal associated with associative recognition memory (identical > recombined rejection) for: (A) young: (i) left posterior parahippocampal gyrus ($x = -26$, $y = -38$, $z = -10$); (ii,iii) left anterior hippocampus ($x = -36$, $y = -24$, $z = -14$) ($x = -26$, $y = -14$, $z = -22$) and (B) old: (i) right anterior hippocampus ($x = 36$, $y = -18$, $z = -16$); (ii) left anterior hippocampus ($x = -30$, $y = -22$, $z = -14$); (iii) left anterior parahippocampal gyrus ($x = -32$, $y = -14$, $z = -32$) subjects. Graph depicts mean percent signal change associated with each group within the region of interest.

Table 1 | BOLD signal increase for the contrast of identical hits > correct recombined rejection in young and older participants.

	Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels	*t*-Score
			X	*Y*	*Z*		
Young	Middle frontal gyrus	L	−40	20	44	927	3.7
	Putamen	R	28	−6	−2	884	3.51
	Juxtapositional lobule cortex	R	6	−10	52	841	3.67
	Lateral occipital cortex	L	−50	−64	38	725	3.53
	Frontal pole	R	40	52	−8	330	3.29
	Frontal pole	L	−20	50	28	253	3.14
	Frontal pole	L	−42	46	6	219	3.11
	Cerebellum	L	−16	−58	−22	208	3.08
	Precentral gyrus	R	60	6	4	101	2.88
	Posterior cingulate gyrus	R	2	−38	2	82	2.93
	Supramarginal gyrus	L	−56	−42	30	71	2.62
	Frontal pole	L	−22	62	4	67	2.82
	Cerebellum	L	−2	−66	−20	56	2.93
	Putamen	L	57	69	34	50	2.72
Young MTL	Posterior parahippocampal gyrus	L	−26	−38	−10	33	2.82
	Hippocampus	L	−26	−14	−22	17	2.65
	Hippocampus	L	−36	−24	−14	13	2.74
Older	Insular cortex	L	−32	−12	14	132	2.91
	Posterior cingulate gyrus	R	8	−24	46	71	2.74
	Occipital fusiform gyrus	L	−20	−68	−16	64	2.76
	Middle frontal gyrus	R	28	28	30	59	2.7
Older MTL	Hippocampus	R	36	−18	−16	10	2.96
	Hippocampus	L	−30	−22	−14	3	2.32
	Anterior parahippocampal gyrus (perirhinal)	L	−32	−14	−32	2	2.24

Results are reported at $p < 0.001$ uncorrected with at least 50 contiguous voxels.

performance. Young adults showed a left lateralized activation involving the anterior hippocampus and posterior parahippocampal gyrus. In contrast, older participants revealed hippocampal involvement bilaterally. In addition to these MTL regions, associative memory performance was also associated with increased activity in a number of cortical and subcortical regions including the middle frontal gyrus, putamen, lateral occipital cortex, precentral gyrus, posterior cingulate gyrus, supramarginal gyrus, and frontal pole in the young adults, as well as the insular cortex, posterior cingulate, occipital fusiform, and middle frontal gyrus in the older adults.

These results suggest a reorganization in the neural correlates of associative recognition memory for compound words with age. Imaging findings from the young group align well with the view that verbal memory processing is supported by a left lateralized distributed network involving anterior regions of the MTL (Binder et al., 2003; Daselaar et al., 2003; Parsons et al., 2006; Ford et al., 2010). More specifically, we found left anterior hippocampal and posterior parahippocampal gyrus activation in this group. A previous study utilized a similar task to the one used in the present study to investigate associative memory processing in young adults and reported recruitment of the left perirhinal cortex (Ford et al., 2010). We found no evidence of left perirhinal cortex recruitment in the young group but did observe a small left perirhinal cortex cluster in the older group. Importantly, bilateral hippocampus recruitment was also present in the older group. To our knowledge, this is the first observation of age-related functional change in the neural correlates of associative recognition memory for compound words. Age-related changes affecting the laterality of MTL activation have previously been observed in functional imaging studies of autobiographical memory retrieval, with predominant left hippocampus recruitment found in young adults compared to bilateral activation in older adults (Maguire and Frith, 2003). We observed a similar age-related left–right shift in MTL activation during successful associative recognition memory for compound words. Involvement of the left anterior hippocampus was observed only in the young group. In the older group, activation of more posterior regions of the hippocampus bilaterally supporting memory performance was found instead.

In addition to changes in MTL activity, we also observed changes in a number of cortical and subcortical brain regions, which have been previously implicated in verbal memory processing, verbal fluency, and naming of objects (Valenstein et al., 1987; Petrides et al., 1993; Salmon et al., 1996; Rosen et al., 2000; Chouinard et al., 2009; Bokde et al., 2010; Lim et al., 2012; Thames et al., 2012; Costa et al., 2013). Recruitment of some of these

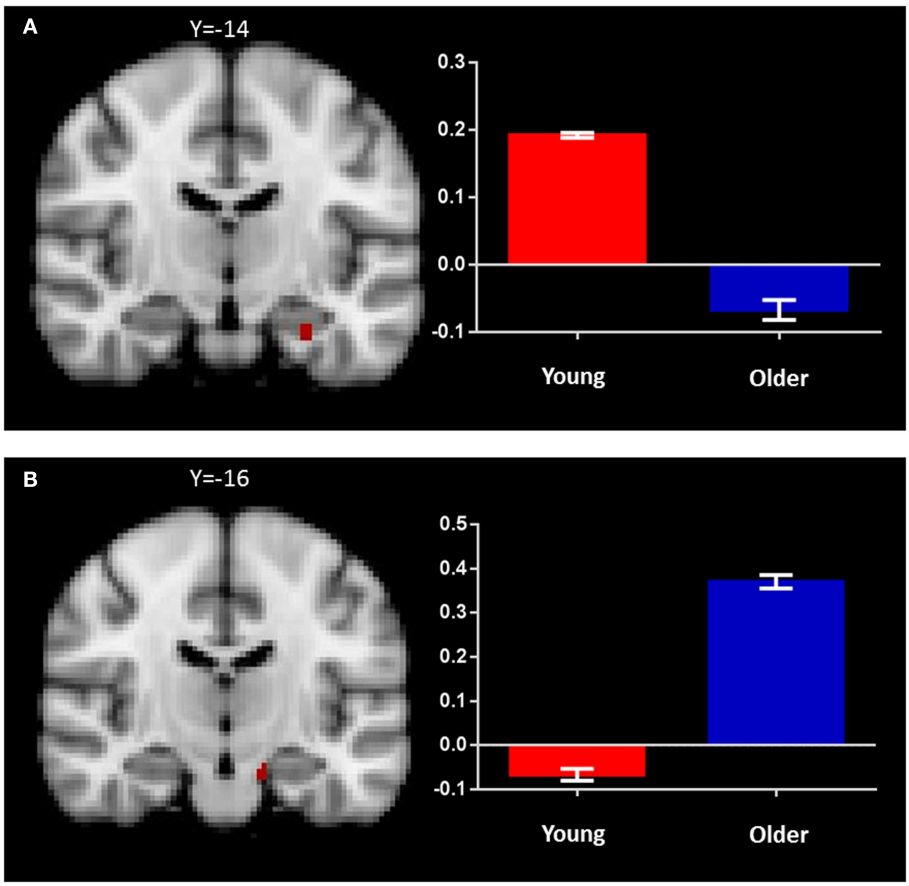


FIGURE 4 | Regions of increased BOLD signal associated with recognition memory (identical > novel) for: (A) young: left anterior hippocampus ($x = -28$, $y = -14$, $z = -24$) and (B) old ($x = -14$, $y = -16$, $z = -22$) subjects. Graph depicts mean percent signal change associated with each group within the region of interest.

regions was age specific. Activation in the putamen, frontal pole, supramarginal gyrus, and lateral occipital cortex was found in the young group only. Regions of activation observed only in the older group included the insular cortex and fusiform gyrus, again regions that have been previously implicated in verbal memory (Paulesu et al., 1993; Grasby et al., 1994; Manes et al., 1999) although the fusiform cortex is generally considered to be involved in memory processing of non-verbal pictorial rather than verbal stimuli (Kim, 2011).

In contrast to associative recognition memory, recognition memory (i.e., correct identification of identical stimuli) differed between groups, with older adults experiencing greater difficulty than young participants on this component of the task. As anticipated, the neural correlates of recognition memory also differed between groups. During this task, young adults recruited the left anterior hippocampus whereas older adults showed involvement of the left hippocampus more posteriorly with additional recruitment of frontal cortical regions bilaterally. In other words, older adults were unable to maintain a level of performance similar to that of young adults despite the recruitment of additional brain regions. The increase in bilateral brain activation with age during memory retrieval has been reported previously and appears to reflect a compensatory process (Reuter-Lorenz and Cappell, 2008; Cappell et al., 2010). Although recognition of recombined stimuli is inherently more difficult than that of identical stimuli, we found an age difference on the recognition performance for the identical but not the recombined component of the task. Whilst we observed a drop in response accuracy between identical and recombined stimuli for the young group, performance in the older group between conditions remained relatively unchanged. Two explanations may underlie this unanticipated result. First, evidence indicates that older adults tend to show a more liberal response pattern in recognition memory tasks compared to young adults (Huh et al., 2006). Frequency of false alarms during recognition memory tasks also tends to rise with task difficulty, regardless of age. Indeed, in this study, the young group showed higher false alarms in the recombined than the identical conditions. The frequency of false alarms, however, remained stable in the older group. This may have been due to the task instructions. Here, correct responses to the instructions ("Have you seen this word before?") necessitated opposing behaviors depending on the stimulus types: "yes" responses to identical stimuli, but

Table 2 | BOLD signal increase for the contrast of identical hits > novel hits in young and older participants.

	Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels	*t*-Score
			X	*Y*	*Z*		
Young	Lateral occipital cortex	L	−46	−64	42	667	3.39
	Middle frontal gyrus	L	−46	18	34	274	3.16
	Frontal pole	R	44	36	20	138	3.03
	Lateral occipital cortex	R	36	−72	46	126	2.74
	Thalamus	R	12	−10	4	121	2.82
	Superior frontal gyrus	R	26	30	54	71	2.95
	Juxtapositional lobule cortex	R	6	−8	48	70	3.19
	Frontal pole	R	10	56	18	68	2.72
	Precuneus cortex	R	4	−56	34	61	2.64
Young MTL	Hippocampus	L	−28	−14	−24	14	2.67
Older	Angular gyrus	L	−50	−56	48	846	3.05
	Superior frontal gyrus	L	−20	20	56	622	3.04
	Lateral occipital cortex	R	40	−64	38	447	3.0
	Middle frontal gyrus	R	36	10	48	245	2.9
	Frontal pole	L	−38	40	6	207	2.89
	Middle frontal gyrus	L	−52	30	24	201	2.86
	Frontal pole	L	−10	64	20	148	2.93
	Middle frontal gyrus	R	44	26	24	83	2.81
	Frontal pole	R	20	52	12	82	2.72
	Precentral gyrus	R	46	4	26	79	2.82
	Frontal pole	L	−18	66	0	76	2.89
	Paracingulate gyrus	L	−12	44	14	64	2.63
	Supramarginal gyrus	L	−60	−46	40	50	2.7
Older MTL	Hippocampus	L	−14	−16	−22	7	2.44

Results are reported at $p < 0.001$ uncorrected with at least 50 contiguous voxels.

"no" responses to recombined stimuli. It is therefore plausible that the response type required in this condition (i.e., having to reject correctly identified recombined stimuli) may have counterbalanced the liberal bias generally observed in the older group and reduced the false alarm responses, thus reducing the between-group difference. Second, close inspection of individual response profiles revealed that three young participants scored at least 2 SDs below the group mean for the recombined condition, contributing to the lack of group difference[1].

The group difference in the patterns of brain activation may represent a functional reorganization and compensation for the decreased efficiency in hippocampal recruitment found as individuals get older. Hippocampal volumes decrease with healthy aging (Raz and Rodrigue, 2006) and are predictive of explicit memory performance in subjects over the age of 60 (Raz et al., 1998; Lye et al., 2004). Loss of synaptic density, rather than neuronal loss, is the main contributor to the volume reduction (Rosenzweig and Barnes, 2003; Burke and Barnes, 2006). Not all hippocampal regions undergo the same changes, however, with anterior regions appearing to be more resilient to age-related degradation than posterior regions (Driscoll et al., 2003). Within this framework, the recruitment of posterior regions of the hippocampus in the older group remains to be investigated further. Age-related reductions in hippocampal activation have been reported during a number of memory tasks using differing methodologies such as encoding of nouns (Daselaar et al., 2003), autobiographical memory retrieval (St Jacques et al., 2012), working memory for complex scenes (Park et al., 2003) and relational encoding in working memory (Mitchell et al., 2000). In addition, memory performance is also affected by the integrity of the connections between MTL and surrounding structures (Hornberger et al., 2012). The reduced activation in the left anterior hippocampus found in the older group accords well with these findings.

The perirhinal cortex and parahippocampal gyrus are components of two dissociable cortical networks with the perirhinal cortex contributing to memory for item information and the parahippocampal gyrus contributing to memory for context (Ranganath and Ritchey, 2012). The parahippocampal gyrus has also been implicated in episodic simulation (Addis et al., 2009). As such, the difference in brain activation may also indicate the use of different mnemonic strategies in the young and older groups. The increased posterior parahippocampal gyrus activation and lack of

[1]Indeed, re-analysis of the behavioral data when these three outliers from the young group are excluded result in a significant between-group difference for the recombined condition.

perirhinal cortex activation in the young group possibly reflects the reliance on mnemonic techniques such as visualization or mental elaboration in this group (e.g., Kondo et al., 2005). In post task debriefings, participants commonly mentioned the use of visualization and association as mnemonic tools to help remember each item. Whether the use of such strategies differed between the two groups was not formally investigated.

Arguably, our findings need to be taken with caution in the view of the uncorrected results reported here. Nevertheless, while the activation clusters in the MTL may appear small, they are in line with those found previously (Staresina and Davachi, 2006). These potential limitations notwithstanding, we have shown that associative recognition memory for compound words is associated with left lateralized MTL structures in young individuals and bilateral MTL structures in their older counterparts. We provide evidence for a functional reorganization of the neural correlates of associative memory processing in the aging brain. These findings have important implications for theoretical models of associative memory processing, in that they support the view that different regions of the MTL are capable of supporting associative recognition memory for verbal stimuli in different stages of life.

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REFERENCES

Addis, D. R., Pan, L., Vu, M.-A., Laiser, N., and Schacter, D. L. (2009). Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imagining and remembering. *Neuropsychologia* 47, 2222–2238. doi:10.1016/j.neuropsychologia.2008.10.026

Binder, J. R., McKiernan, K. A., Parsons, M. E., Westbury, C. F., Possing, E. T., Kaufman, J. N., et al. (2003). Neural correlates of lexical access during visual word recognition. *J. Cogn. Neurosci.* 15, 372–393. doi:10.1162/089892903321593108

Bokde, A. L., Karmann, M., Born, C., Teipel, S. J., Omerovic, M., Ewers, M., et al. (2010). Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. *J. Alzheimers Dis.* 21, 103–118. doi:10.3233/JAD-2010-091054

Burke, S. N., and Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nat. Rev. Neurosci.* 7, 30–40. doi:10.1038/nrn1809

Bussey, T. J., Saksida, L. M., and Murray, E. A. (2005). The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. *Q. J. Exp. Psychol. B* 58, 269–282. doi:10.1080/02724990544000004

Cabeza, R. (2001). Cognitive neuroscience of aging: contributions of functional neuroimaging. *Scand. J. Psychol.* 42, 277–286. doi:10.1111/1467-9450.00237

Cappell, K. A., Gmeindl, L., and Reuter-Lorenz, P. A. (2010). Age differences in prefontal recruitment during verbal working memory maintenance depend on memory load. *Cortex* 46, 462–473. doi:10.1016/j.cortex.2009.11.009

Chouinard, P. A., Whitwell, R. L., and Goodale, M. A. (2009). The lateral-occipital and the inferior-frontal cortex play different roles during the naming of visually presented objects. *Hum. Brain Mapp.* 30, 3851–3864. doi:10.1002/hbm.20812

Christensen, H. (2001). What cognitive changes can be expected with normal ageing? *Aust. N. Z. J. Psychiatry* 35, 768–775. doi:10.1046/j.1440-1614.2001.00966.x

Costa, A., Oliveri, M., Barban, F., Bonni, S., Koch, G., Caltagirone, C., et al. (2013). The right frontopolar cortex is involved in visual-spatial prospective memory. *PLoS ONE* 8:e56039. doi:10.1371/journal.pone.0056039

Daselaar, S. M., Veltman, D. J., Rombouts, S. A., Raaijmakers, J. G., and Jonker, C. (2003). Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. *Brain* 126, 43–56. doi:10.1093/brain/awg005

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr. Opin. Neurobiol.* 16, 693–700. doi:10.1016/j.conb.2006.10.012

Driscoll, I., Hamilton, D. A., Petropoulos, H., Yeo, R. A., Brooks, W. M., Baumgartner, R. N., et al. (2003). The aging hippocampus: cognitive, biochemical and structural findings. *Cereb. Cortex* 13, 1344–1351. doi:10.1093/cercor/bhg081

Ford, J. H., Verfaellie, M., and Giovanello, K. S. (2010). Neural correlates of familiarity-based associative retrieval. *Neuropsychologia* 48, 3019–3025. doi:10.1016/j.neuropsychologia.2010.06.010

Giovanello, K. S., and Schacter, D. L. (2012). Reduced specificity of hippocampal and posterior ventrolateral prefrontal activity during relational retrieval in normal aging. *J. Cogn. Neurosci.* 24, 159–170. doi:10.1162/jocn_a_00113

Grasby, P. M., Frith, C. D., Friston, K. J., Simpson, J., Fletcher, P. C., Frackowiak, R. S., et al. (1994). A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. *Brain* 117(Pt 6), 1271–1282. doi:10.1093/brain/117.6.1271

Harris, M. A., and Wolbers, T. (2012). Ageing effects on path integration and landmark navigation. *Hippocampus* 22, 1770–1780. doi:10.1002/hipo.22011

Head, D., and Isom, M. (2010). Age effects on wayfinding and route learning skills. *Behav. Brain Res.* 209, 49–58. doi:10.1016/j.bbr.2010.01.012

Hornberger, M., Wong, S., Tan, R., Irish, M., Piguet, O., Kril, J., et al. (2012). In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain* 135, 3015–3025. doi:10.1093/brain/aws239

Huh, T. J., Kramer, J. H., Gazzaley, A., and Delis, D. C. (2006). Response bias and aging on a recognition memory task. *J. Int. Neuropsychol. Soc.* 12, 1–7. doi:10.1017/S1355617706060024

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., et al. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am. J. Neuroradiol.* 19, 659–671.

Jack, C. R. Jr., Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., et al. (1998). Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology* 51, 993–999. doi:10.1212/WNL.51.4.993

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuroimage* 54, 2446–2461. doi:10.1016/j.neuroimage.2010.09.045

Kondo, Y., Suzuki, M., Mugikura, S., Abe, N., Takahashi, S., Iijima, T., et al. (2005). Changes in brain activation associated with use of a memory strategy: a functional MRI study. *Neuroimage* 24, 1154–1163. doi:10.1016/j.neuroimage.2004.10.033

Konkel, A., Warren, D. E., Duff, M. C., Tranel, D. N., and Cohen, N. J. (2008). Hippocampal amnesia impairs all manner of relational memory. *Front. Hum. Neurosci.* 2:15. doi:10.3389/neuro.09.015.2008

Lim, T. S., Hong, Y. H., Choi, J. Y., Kim, H. S., and Moon, S. Y. (2012). Functional investigation of bilateral posterior cingulate gyri using multivoxel MR spectroscopy. *Eur. Neurol.* 67, 279–286. doi:10.1159/000336834

Lye, T. C., Piguet, O., Grayson, D. A., Creasey, H., Ridley, L. J., Bennett, H. P., et al. (2004). Hippocampal size and memory function in the ninth and tenth decades of life: the Sydney Older Persons Study. *J. Neurol. Neurosurg. Psychiatry* 75, 548–554. doi:10.1136/jnnp.2003.010223

Maguire, E. A., and Frith, C. D. (2003). Aging affects the engagement of the hippocampus during autobiographical memory retrieval. *Brain* 126, 1511–1523. doi:10.1093/brain/awg157

Manes, F., Springer, J., Jorge, R., and Robinson, R. G. (1999). Verbal memory impairment after left insular cortex infarction. *J. Neurol. Neurosurg. Psychiatry* 67, 532–534. doi:10.1136/jnnp.67.4.532

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn. Sci.* 11, 126–135. doi:10.1016/j.tics.2006.12.003

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Montaldi, D., Grigor, J., Gummer, A., et al. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus* 14, 763–784. doi:10.1002/hipo.10211

Mitchell, K. J., Johnson, M. K., Raye, C. L., and D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. *Brain Res. Cogn. Brain Res.* 10, 197–206. doi:10.1016/S0926-6410(00)00029-X

Nyberg, L., Maitland, S. B., Ronnlund, M., Backman, L., Dixon, R. A., Wahlin, A., et al. (2003). Selective adult age differences in an age-invariant multifactor model of declarative memory. *Psychol. Aging* 18, 149–160. doi:10.1037/0882-7974.18.1.149

Park, D. C., Welsh, R. C., Marshuetz, C., Gutchess, A. H., Mikels, J., Polk, T. A., et al. (2003). Working memory for complex scenes: age differences in frontal and hippocampal activations. *J. Cogn. Neurosci.* 15, 1122–1134. doi:10.1162/089892903322598094

Parsons, M. W., Haut, M. W., Lemieux, S. K., Moran, M. T., and Leach, S. G. (2006). Anterior medial temporal lobe activation during encoding of words: FMRI methods to optimize sensitivity. *Brain Cogn.* 60, 253–261. doi:10.1016/j.bandc.2005.07.010

Paulesu, E., Frith, C. D., and Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature* 362, 342–345. doi:10.1038/362342a0

Petrides, M., Alivisatos, B., Meyer, E., and Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc. Natl. Acad. Sci. U.S.A.* 90, 878–882. doi:10.1073/pnas.90.3.878

Ranganath, C., and Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nat. Rev. Neurosci.* 13, 713–726. doi:10.1038/nrn3338

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., and Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. *Neuropsychology* 12, 95–114. doi:10.1037/0894-4105.12.1.95

Raz, N., and Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci. Biobehav. Rev.* 30, 730–748. doi:10.1016/j.neubiorev.2006.07.001

Raz, N., Rodrigue, K. M., Head, D., Kennedy, K. M., and Acker, J. D. (2004). Differential aging of the medial temporal lobe: a study of a five-year change. *Neurology* 62, 433–438. doi:10.1212/01.WNL.0000106466.09835.46

Reuter-Lorenz, P. A., and Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Curr. Dir. Psychol. Sci.* 17, 177–182. doi:10.1111/j.1467-8721.2008.00570.x

Ronnlund, M., Nyberg, L., Backman, L., and Nilsson, L. G. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychol. Aging* 20, 3–18. doi:10.1037/0882-7974.20.1.3

Rosen, H. J., Ojemann, J. G., Ollinger, J. M., and Petersen, S. E. (2000). Comparison of brain activation during word retrieval done silently and aloud using fMRI. *Brain Cogn.* 42, 201–217. doi:10.1006/brcg.1999.1100

Rosenzweig, E. S., and Barnes, C. A. (2003). Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog. Neurobiol.* 69, 143–179. doi:10.1016/S0301-0082(02)00126-0

Salmon, E., Van der Linden, M., Collette, F., Delfiore, G., Maquet, P., Degueldre, C., et al. (1996). Regional brain activity during working memory tasks. *Brain* 119(Pt 5), 1617–1625. doi:10.1093/brain/119.5.1617

Schaie, K. W. (2005). *Developmental Influences on Adult Intelligence: The Seattle Longitudinal Study*. New York: Oxford University Press.

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21. doi:10.1136/jnnp.20.1.11

Shaw, S. M., Helmes, E., and Mitchell, D. (2006). Age-related change in visual, spatial and verbal memory. *Australas. J. Ageing* 25, 14–19. doi:10.1111/j.1741-6612.2006.00134.x

Small, S. A., Tsai, W. Y., DeLaPaz, R., Mayeux, R., and Stern, Y. (2002). Imaging hippocampal function across the human life span: is memory decline normal or not? *Ann. Neurol.* 51, 290–295. doi:10.1002/ana.10105

St Jacques, P. L., Rubin, D. C., and Cabeza, R. (2012). Age-related effects on the neural correlates of autobiographical memory retrieval. *Neurobiol. Aging* 33, 1298–1310. doi:10.1016/j.neurobiolaging.2010.11.007

Staresina, B. P., and Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *J. Neurosci.* 26, 9162–9172. doi:10.1523/JNEUROSCI.2877-06.2006

Thames, A. D., Foley, J. M., Wright, M. J., Panos, S. E., Ettenhofer, M., Ramezani, A., et al. (2012). Basal ganglia structures differentially contribute to verbal fluency: evidence from human immunodeficiency virus (HIV)-infected adults. *Neuropsychologia* 50, 390–395. doi:10.1016/j.neuropsychologia.2011.12.010

Troyer, A. K., D'Souza, N. A., Vandermorris, S., and Murphy, K. J. (2011). Age-related differences in associative memory depend on the types of associations that are formed. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 18, 340–352. doi:10.1080/13825585.2011.553273

Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K. M., Day, A., and Watson, R. T. (1987). Retrosplenial amnesia. *Brain* 110(Pt 6), 1631–1646. doi:10.1093/brain/110.6.1631

West, M. J. (1993). Regionally specific loss of neurons in the aging human hippocampus. *Neurobiol. Aging* 14, 287–293. doi:10.1016/0197-4580(93)90113-P

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APPENDIX

Table A1 | Example list of words used in the intra-item associative memory task.

Study		Test		
		Identical	**Recombined**	**Novel**
WORDS USED AS RECOMBINED ITEMS AT TEST				
Bluebell	Hummingbird	Sandstorm	Bluebird	Underground
Postcard	Trademark	Snowman	Postmark	Sunlight
Playroom	Checkmate	Needlepoint	Playmate	Lapdog
Fireboat	Marketplace	Artwork	Fireplace	Spacecraft
Fatherland	Neighborhood	Meatball	Fatherhood	Jumpsuit
Downstairs	Waterfall	Brainpower	Downfall	Headdress
Earthmover	Silkworm	Cupcake	Earthworm	Eyewitness
Mainframe	Slipstream	Shuffleboard	Mainstream	Foresight
Newspaper	Bandstand	Handbag	Newsstand	Keystone
Outlook	Trapdoors	Horserace	Outdoors	Crossword
Stardust	Bracelet	Blowtorch	Starlet	Turntable
Nightshade	Hubcap	Sidewalk	Nightcap	Breakfast
Facemask	Forklift	Smokestack	Facelift	Getaway
Beehive	Housekeeper	Flyscreen	Beekeeper	Armrest
Hedgerow	Warthog	Boxcar	Hedgehog	Coalpit
Backbone	Raindrop	Footstep	Backdrop	Hourglass
Bottleneck	Paintbrush	Buttonhole	Bottlebrush	Spymaster
Steamroller	Longboat	Motorcycle	Steamboat	Drumbeat
Shortcut	Gingerbread	Courtship	Shortbread	Waistcoat
Skydive	Mudlark	Vineyard	Skylark	Joystick
WORDS USED AS IDENTICAL ITEMS AT TEST				
Sandstorm	Buttonhole			
Snowman	Boxcar			
Needlepoint	Courtship			
Artwork	Blowtorch			
Meatball	Footstep			
Brainpower	Vineyard			
Cupcake	Sidewalk			
Shuffleboard	Smokestack			
Handbag	Motorcycle			
Horserace	Flyscreen			

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Aging-related episodic memory decline: are emotions the key?

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Episodic memory refers to the recollection of personal experiences that contain information on what has happened and also where and when these events took place. Episodic memory function is extremely sensitive to cerebral aging and neurodegerative diseases. We examined episodic memory performance with a novel test in young ($N = 17$, age: 21–45), middle-aged ($N = 16$, age: 48–62) and aged but otherwise healthy participants ($N = 8$, age: 71–83) along with measurements of trait and state anxiety. As expected we found significantly impaired episodic memory performance in the aged group as compared to the young group. The aged group also showed impaired working memory performance as well as significantly decreased levels of trait anxiety. No significant correlation between the total episodic memory and trait or state anxiety scores was found. The present results show an age-dependent episodic memory decline along with lower trait anxiety in the aged group. Yet, it still remains to be determined whether this difference in anxiety is related to the impaired episodic memory performance in the aged group.

Keywords: aging, anxiety, episodic memory, depression, working memory

INTRODUCTION

Episodic memory refers to the conscious recollection of a personal experience that contains information on what has happened and also where and when it happened (Tulving, 1983). Remembering a personal experience might also be accompanied by the remembrance of specific perceptions, emotions, and thoughts one had during a particular experience (Tulving, 2002). Episodic memory deficits are observed after medial temporal lobe injury (Nyberg et al., 1996) which includes important memory structures such as the hippocampus (Burgess et al., 2002) and amygdala (Markowitsch and Staniloiu, 2011) but also after lesions to the frontal cortex (Kirchhoff et al., 2000) and diencephalic structures, such as the mediodorsal thalamus and the mammillary bodies (Tsivilis et al., 2008; Wolff et al., 2008).

Episodic memory function is also extremely sensitive to cerebral aging (Shing et al., 2010; Nyberg et al., 2012), neurodegenerative (Williams-Gray et al., 2006; Dubois et al., 2007), and psychiatric diseases (Dere et al., 2010). Cross-sectional studies have indicated that the age-dependent decline in episodic memory function starts as early as at the age of 30 (Park et al., 2002), while longitudinal studies propose a later onset between ages 65 and 70 years (Rönnlund et al., 2005). Age-dependent memory decline seems to be paralleled by volume reductions in brain structures important for memory performance, including the medial temporal lobe (Persson et al., 2006), the hippocampus (Rajah et al., 2010), and the prefrontal cortex (Van Petten et al., 2004). Although, it is well known that the amygdala, besides its prominent role in the generation of emotions, is also involved in memory consolidation after fear conditioning (LeDoux, 2007) and emotional events (McIntyre et al., 2003; McGaugh, 2004), its role during age-dependent memory decline has attracted surprisingly fewer research activity.

The role of emotions in the decline of episodic memory function that is seen in the course of physiological aging is still poorly understood. Although emotions are not necessarily an integral component of episodic memory, emotional arousal, or psychosocial stress induced in the laboratory during the encoding of episodic information can facilitate episodic memory consolidation into long-term memory (Wolf, 2012).

It has been also proposed that emotions might be a trigger for episodic memory formation (Libkuman et al., 2004; Dere et al., 2010; Kensinger et al., 2011), play a role in the binding of different features of an event into an integrated episodic memory (Nashiro and Mather, 2011), mediate the self-relevant aspect of an episodic memory (Wheeler et al., 1997) and might also determine their durability in a way that strong emotional activation leads to long-durable episodic memories, while weak emotional activation leads only to short-durable episodic memories (Dere et al., 2010). In line with this proposition it has been found that emotions improve the ability of aged individuals to retrieve more details of an event as well as its context (Kensinger, 2009). There is also evidence suggesting that the

processing of emotional stimuli and the physiological arousal mediated by the autonomic system in response to emotionally negative stimuli is compromised in aged individuals (Kaszniak and Menchola, 2012). In this study, we investigated the possibility that aging-induced episodic memory decline might be due to changes in emotionality e.g., in terms of the response to stimuli that have been associated with an emotionally arousing context story.

In order to test the emotionality hypothesis of aging-induced episodic memory impairments, we measured episodic memory in young, middle-aged, and aged participants with a novel paradigm which measures memory for different stimuli, the temporal order of their presentation as well as the spatial locations where they have been presented. This test also measures the ability to establish new episodic memories. We further assessed trait and state anxiety in the 3 groups in order to determine if impairments in episodic memory performance are indeed correlated with decreased levels of trait and/or state anxiety.

Given that depressive symptoms are common in the aged population and are associated with cognitive impairments including working memory deficits (Bornstein et al., 1991; Nebes et al., 2000) we additionally probed whether aging-induced episodic memory decline would be associated with impairments in working memory or depressive symptoms.

MATERIALS AND METHODS

PARTICIPANTS

Forty-one healthy adult volunteers (♀ = 22, ♂ = 19) participated in this study. The participants were recruited from University Pierre and Marie Curie Paris 6 students and employees and among healthy relatives of patients attending the geriatric hospital Charles Foix in Ivry-Sur-Seine, France. The participants were aged between 21 and 83 years. They were divided into three groups of young ($N = 17$, mean: 26.76 ± 1.69, age range: 21–45), middle-aged ($N = 16$, mean: 55.31 ± 1.06, age range: 48–62) and aged participants ($N = 8$, mean: 79.13 ± 1.33, age range: 71–83).

None of the participants reported a psychiatric record, history of vascular, psychiatric, neurological, motor or oncologic disease, psychopharmacologic or hormonal therapy or any other health issue that would prohibit their testing. All participants had a corrected to normal vision and audition.

The groups were comparable regarding their sociodemographic and educational background. The study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants. All experimental procedures have been approved by the local ethical committee of the University Pierre and Marie Curie Paris 6.

EXPERIMENTAL DESIGN

In a reverse translational approach by Pause et al. (2010) the rationale and principles of the episodic-like memory test for rodents (Dere et al., 2005a,b; Kart-Teke et al., 2006) have been adapted to humans. We developed a paradigm that measures the spatiotemporal memory for emotional and neutral pictures presented on an eight-quadrant computer-screen task (Pause et al., 2010). This test has been further developed to be applicable to aged individuals and patient populations.

General procedure

The total experiment including the presentation of general information about the experiment, the completion of the participant questionnaire, the neuropsychological testing as well as the episodic memory test had a total duration of approximately 2.5 h. However, the net time of testing was approximately 65 min. The participants received 3 pauses of 2×20 min and 1×45 min in the course of the 2.5 h total duration in order to minimize possible effects of tiredness and fatigue on test performance in the older individuals. **Figure 1** gives overview of the different phases of the experiment, their sequence, and the approximate duration of each test.

First the participant was informed about the general procedure of the experiment without providing an explicit statement that he or she is participating in a memory experiment or had to retain the information presented during the course of the experiment. It is important to note that no explicit information about the purpose of the test was given. Instead the participants were informed that "The aim of this study is to investigate the effects of imagination on visual perception and attention." Thereafter, the participants were asked to complete a standard participant questionnaire including questions about the current and past health status, current and past medication, history of mental diseases, etc. After that the participants working memory for series of numbers was tested using a subtest of the WAIS-R. Immediately thereafter the participants performed the episodic memory test consisting of 3 slide presentations followed by an episodic memory test as described in detail below. Immediately after the third slide presentation, the participants were asked to complete the state anxiety subtest of the STAI (Spielberger et al., 1970). Finally, after the participants had completed the episodic memory test, the Goldberg trait anxiety, and depression scale was performed (Goldberg et al., 1988).

THE EPISODIC MEMORY TEST

This test is based on the "what, where, and when" paradigm (Clayton and Dickinson, 1999; Dere et al., 2005a) that allows to measure the core elements (content, temporal, and spatial context of an unique event) of episodic memory. The present test is designed to measure integrated memories for "what, where, and when" operationalized as "stimulus-position-trial" associations. The test does not allow the assessment of the individual components of episodic memory in terms of content, spatial, and temporal order memory.

Each participant received 3 presentation trials using the Presentation® software Version 12 (Neurobehavioral Systems, CA, USA) and an episodic memory test (recall of 27 different stimulus-position-trial associations). The 3 trials were embedded into a context story (see below) with emotional content. This context story was divided into 3 parts according to the 3 trials. Each part of the context story was narrated by the experimenter to the participant immediately before the presentation of the corresponding presentation trial. Each presentation trial



FIGURE 1 | Experimental design. Overview of the experimental design, the order of tests applied, presentation times of the slides, and the approximate duration of each experimental phase.

consisted of 12 slides. Each slide was presented for 8 s and was followed by the presentation of a fixation cross for 2 s. The first slide showed a background scene with an empty place surrounded by shops (**Figure 2A**). This place was virtually divided into a 3 × 3 matrix with 9 different positions for the presentation of stimuli (**Figure 3C**). The center position was not used for the presentation of stimuli. The second slide consisted of the same background scene including 4 context story-relevant and 4 context story non-relevant stimuli presented within the 3 × 3 matrix (**Figure 2B**). Context story-relevant stimuli were drawings of 4 men wearing suits and having slightly different postures (**Figure 2B**). Stimuli not relevant to the context story consisted of drawings of 4 pigeons (**Figure 2B**). During the slides 3–10 each stimuli position was presented individually for 8 s while the reminder of the background scene including the other stimuli were darkened (**Figures 2C,D**). Each slide was followed by the presentation of a gray slide for 2 s showing a plus-shaped fixation cross at the center. This slide ensured the saccadic resetting of the participants view back to the center of the slide before the next individual position was presented. Slide 11 again presented the complete scene including context story-relevant and non-relevant stimuli. This slide was followed by the presentation of the background scene without stimuli. After a delay of 20 min the second presentation trial was performed. This was identical to the first trial, except that drawings of women were presented instead of men (**Figures 2E,F**). Two of the context story-relevant stimuli (women) were presented at positions already used during the first trial for the placement of context story-relevant stimuli (men), while the remaining 2 context story relevant stimuli were placed at positions which contained context story non-relevant stimuli (pigeons).

After another delay of 20 min the participants viewed the third presentation trial (**Figure 3A**). The third trial was identical to the first 2 presentation trials except that the 4 context story-relevant stimuli consisted of 2 men (in the following referred to as "old" stimuli with respect to the temporal order of the 2 previous trials) and 2 women "recent" stimuli. Additionally one "old" and one "recent" stimuli were presented at a position which was not used for the placement of context story-relevant stimuli during their initial presentation. Thus one "old" and one "recent" stimuli had been displaced to a "novel" position. These stimuli

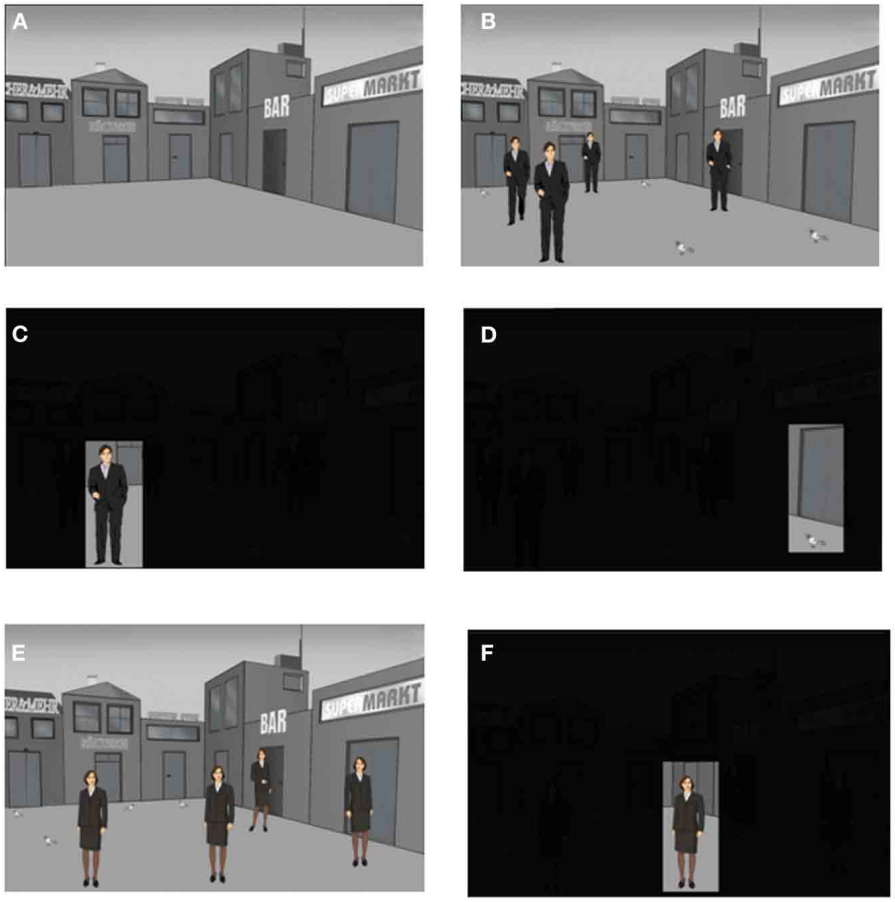


FIGURE 2 | The episodic memory test: presentation trials 1 and 2. Each presentation trial is composed of a series of 12 slides. Each slide is presented for 8 s and is followed by the presentation of a fixation cross for 2 s. Schematic drawings of men (presentation trial 1) or woman (presentation trial 2) are used as context story-relevant stimuli while pigeons are used as context story-non relevant stimuli. **(A)** The first slide of each presentation trial shows the background scene without context story-relevant and non-relevant stimuli. **(B)** Presentation of the 8 positions with 4 men as context story-relevant stimuli on the second slide of trial 1. **(C)** Example for the presentation of a single man-position stimulus during the presentation of the slides 3–10 on trial 1. **(D)** Example for the presentation of a single pigeon-position stimulus during the presentation of the slides 3–10 on trials 1 or 2. **(E)** Presentation of the 8 positions with 4 women as context story-relevant stimuli on the second slide of trial 1. **(F)** Example for the presentation of a single women-position stimulus during the presentation of the slides 3–10 on trial 2.

were referred to as "old displaced" and "recent displaced" stimuli (**Figure 3B**).

Sixty minutes after the third trial the episodic memory test was performed. Here, the participants were asked to recall each of the 27 stimulus-position-trial associations that have been formed during the 3 presentation trials. The sequence of memory tests for the 3 presentation trials was 3-1-2. First the 9 stimulus-position-trial associations of trial 3 were tested, followed by the tests for trials 1 and finally 2. During the test the participant was presented with the background scene without context story-relevant or non-relevant stimuli. The place was divided into a matrix of 9 positions.

Each episodic memory test for individual trials (1, 2, or 3) consisted of 18 slides. Each individual position, marked with red color, was presented for 2 s (**Figure 3C**). Thereafter, a slide appeared asking whether the participant remembered to have seen an empty place, a pigeon, a woman, or a man at this position during that particular trial. On the bottom of this slide the 4 choice options were presented as images. The participant could select the right answer by clicking on the corresponding stimuli (**Figure 3D**). The slide was presented until the participant made a decision. The responses of the participant were automatically recorded and transferred to an Excel® output file. Please note that this procedure allowed the measurement of a memory for what, where, and when in terms of stimulus-position-trial associations with a minimum of verbal requirements allowing the testing of patients with impairments in speech production.

CONTEXT STORY

The context story was divided into 3 parts which were narrated by the experimenter before each presentation trial and had an emotionally arousing content. Before the experimenter narrated each

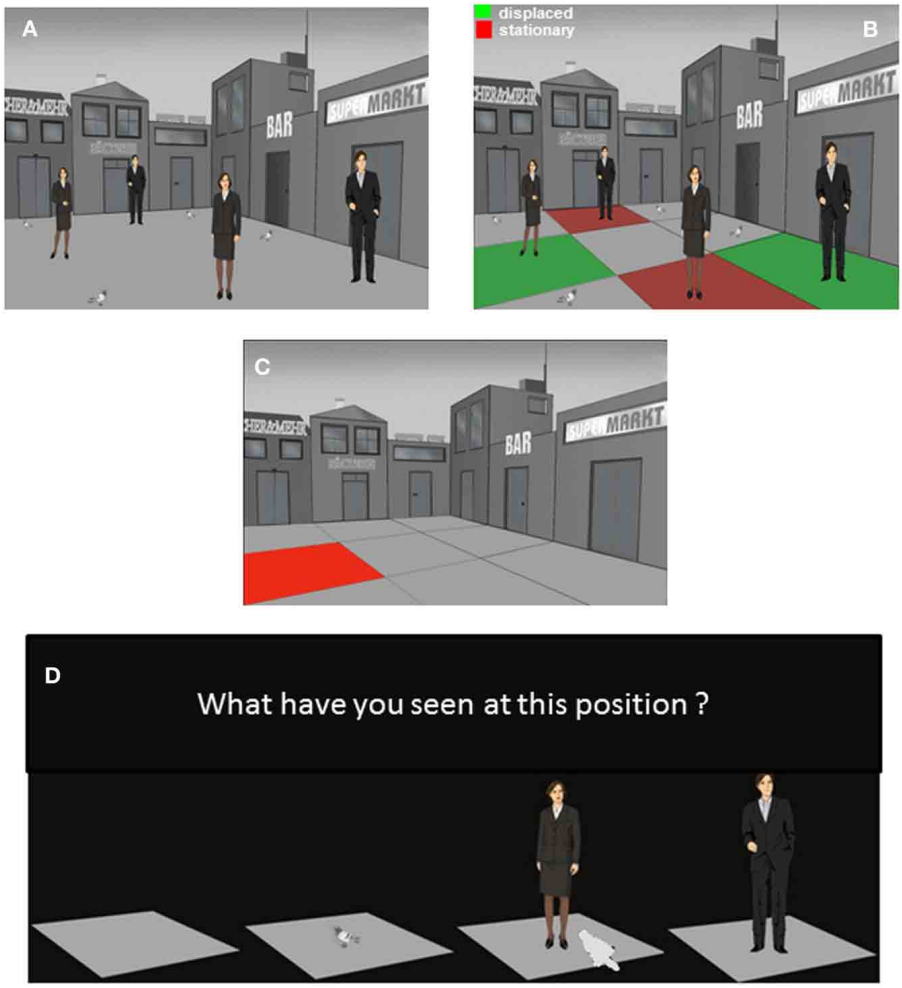


FIGURE 3 | The episodic memory test: presentation trial 3 and test trial. **(A)** Presentation trial 3 where human stimuli from trial 1 and 2 are presented together. Depicted are the 4 positions with human stimuli as context story-relevant stimuli and the 4 position with context story non-relevant stimuli. **(B)** One "old" man and one "recent" woman stimuli were displaced to an unfamiliar position not used during the corresponding presentation trials 1 or 2. Additionally, one "old" men and one "recent" woman stimuli were presented at familiar positions already used during the corresponding presentation trials 1 or 2. The red and green coloring of the quadrants with human stimuli was made for representational purposes and has not been presented to the participants. **(C)** Episodic memory test where participants have to remember the stimulus-position-trial associations formed during the 3 presentation trials. First the positions for the test trial were probed; thereafter the ones for the first trial and finally the ones for the second trial were tested. There were 27 questions in total. On the test trial only the background scene was presented without stimuli. The scene was divided into 9 quadrants. Each of the 9 quadrants was colored and presented individually. **(D)** Thereafter, a slide with the question "What have you seen on this position" and the corresponding response alternatives was presented. The participant was asked to select via mouse click the stimulus which he or she was remembering to be presented on that particular position during a particular presentation trial.

part of the context story the participant was asked to "Please try to imagine the situation."

Part 1

"Please try to imagine the following situation. You are in a foreign town for 3 days. On the first day you take a walk and reach a small place with little shops and pigeons. You see 4 men in black suits. You recognize these men. You remember to have seen their faces before. They are members of a terrorist group, who had recently attempted to commit a poison gas attack to prevent a political conference. You feel that your heart is beating faster. This attack had been prevented at the very latest moment. If it had been successful, there would have been hundreds of victims. You are quite sure that these men belong to this terrorist group. You now feel cold. You now have goose bumps. You are wondering why these men are here and what they have in mind. You are scared and you think about the cruel and unscrupulous crimes that have been committed by these men in the past.

Then the experimenter asked whether the participant had been able to imagine the situation: "Can you imagine the situation? In the following I will show you the close-ups of the place with

the 4 terrorists. When viewing the close-ups please try to imagine what other crimes these people might have committed in the past."

Part 2

"Please try to imagine the following situation." This is your second day in the foreign town. During a walk you revisit the place with the small shops and the pigeons. This time you encounter 4 women. Again you are sure that you have seen these women before. There was a report on a group of women who have planned a bomb attack to the city hall in the local news this morning. You begin to sweat. This assault could only be stopped seconds before the detonation of the bomb. You are sure that these women are the terrorists who have planned and initiated this assault. Your heart beats faster and your palms are cold. You wonder why these women are here right now. You are scared and you think about the brutal and bloody crimes these women might have committed in the past.

"Can you imagine this situation? In the following I will show you the close-ups of the place with the 4 terrorists. When viewing the close-ups please try to imagine what other crimes these people have committed in the past."

Part 3

"Please try to imagine the following situation". This is your third day in the town. During a walk you revisit the place with the small shops and the pigeons. This time you see 2 men and 2 woman. You are sure that you have seen these men and woman on the previous occasions. You are breathing faster. You remember to have seen these people in the morning news. It was said that yesterday evening these people have committed an assault to the central station. You remember the pictures of the destruction and the injured victims you saw this morning in the news. While realizing that you are now very close to these dangerous people you are getting horrified. You are feeling sick and your hands are shivering. You feel insecure and you think about the brutal and bloody crimes these people might have committed in the past.

"Can you imagine this situation? In the following I will show you the close-ups of the place with the 4 terrorists. When viewing the close-ups please try to imagine what terrible consequences the attack to the central station might have for the injured innocents."

STATISTICAL PROCEDURES

Statistical analysis was performed with the program SigmaStat 3.1® (Sysstat Software Inc.). All variables have been initially analyzed with the Kolmogorov–Smirnov test to know whether the data varies significantly from the pattern expected if the data was drawn from a population with a normal distribution. Furthermore, the Levene test was performed to probe the homogeneity of variances across groups. Variables that failed the Kolmogorov–Smirnov or the Levene test were analyzed with nonparametric statistics using the Kruskal–Wallis one-way analysis of variance on ranks and Mann–Whitney rank sum tests for pair-wise multiple comparisons. Variables that passed the normality test were analyzed by means of One-Way ANOVA's and Holm–Sidak and Student *t*-tests for pair-wise multiple comparisons. Correlations between the state and trait anxiety measures and the different episodic memory measures (total score, human stimuli score, pigeon stimuli score, and the scores for the trials 1–3) were performed using both Pearson pair-wise and Spearman-rank correlation procedures in dependence of the distribution of the variables. All *P*-values given are two-tailed, and are considered to be significant when $P < 0.05$ or in the case of the Holm–Sidak tests when the *P*-value obtained was lower than the adjusted *P*-level of significance.

RESULTS

EPISODIC MEMORY PERFORMANCE

Total episodic memory score

In this experiment we investigated whether a novel test of episodic memory is suited to detect age-related decrements in episodic memory performance by testing 3 different age groups consisting of young [21–45], middle-aged [48–62], and aged [71–83] healthy adult participants. In order to know whether the groups differ in terms of episodic memory performance we calculated a total episodic memory score that could vary between 0 and 27 correctly remembered stimulus-position-trial associations.

As expected a One-Way ANOVA revealed that the performance of the 3 groups was indeed significantly different from each other (Kolmogorov–Smirnov test: $P > 0.05$, Levene test $P > 0.05$; ANOVA: $F_{(2,\ 38)} = 7.785$, $P = 0.001$, **Figure 4A**). In order to know which groups performed significantly different from each other, we computed *post-hoc* tests using the Holm–Sidak method. We found that the young group had significantly higher episodic memory scores as compared to both the middle ($T = 2.675$; $P = 0.011$, significant at the critical *P*-level of $P = 0.025$) and aged groups ($T = 3.72$; $P < 0.001$, significant at the critical *P*-level of $P = 0.017$). The latter two groups performed not significantly different from each other ($P > 0.05$).

This result suggest that episodic memory performance is significantly better in young individuals aged between 21 and 45 years as compared to individuals aged between 48 and 62 or older participants.

Episodic memory performance for individual presentation trials

We also analyzed whether the groups would differ regarding their episodic memory scores for the three presentation trials. We expected that the episodic memory performance for trial 1 would be significantly different between the groups because the delay between episodic memory encoding and the recollection of the episodic memory formed was longest >2 h for the first trial as compared to the second and third trials. As predicted, we found that the 3 age groups differed significantly regarding the number of correctly remembered stimulus-position associations for trial 1 (Kolmogorov–Smirnov test: $P > 0.05$, Levene test: $P > 0.05$; ANOVA: $F_{(2,\ 38)} = 7.056$, $P = 0.002$; **Figure 4B**).

Pair-wise *post-hoc* Holm–Sidak tests revealed that the performance of the aged group during the retrieval of the information for trial 1 was significantly worse as compared to both the young ($T = 3.756$; $P = 0.000578$, significant at the critical *P*-level

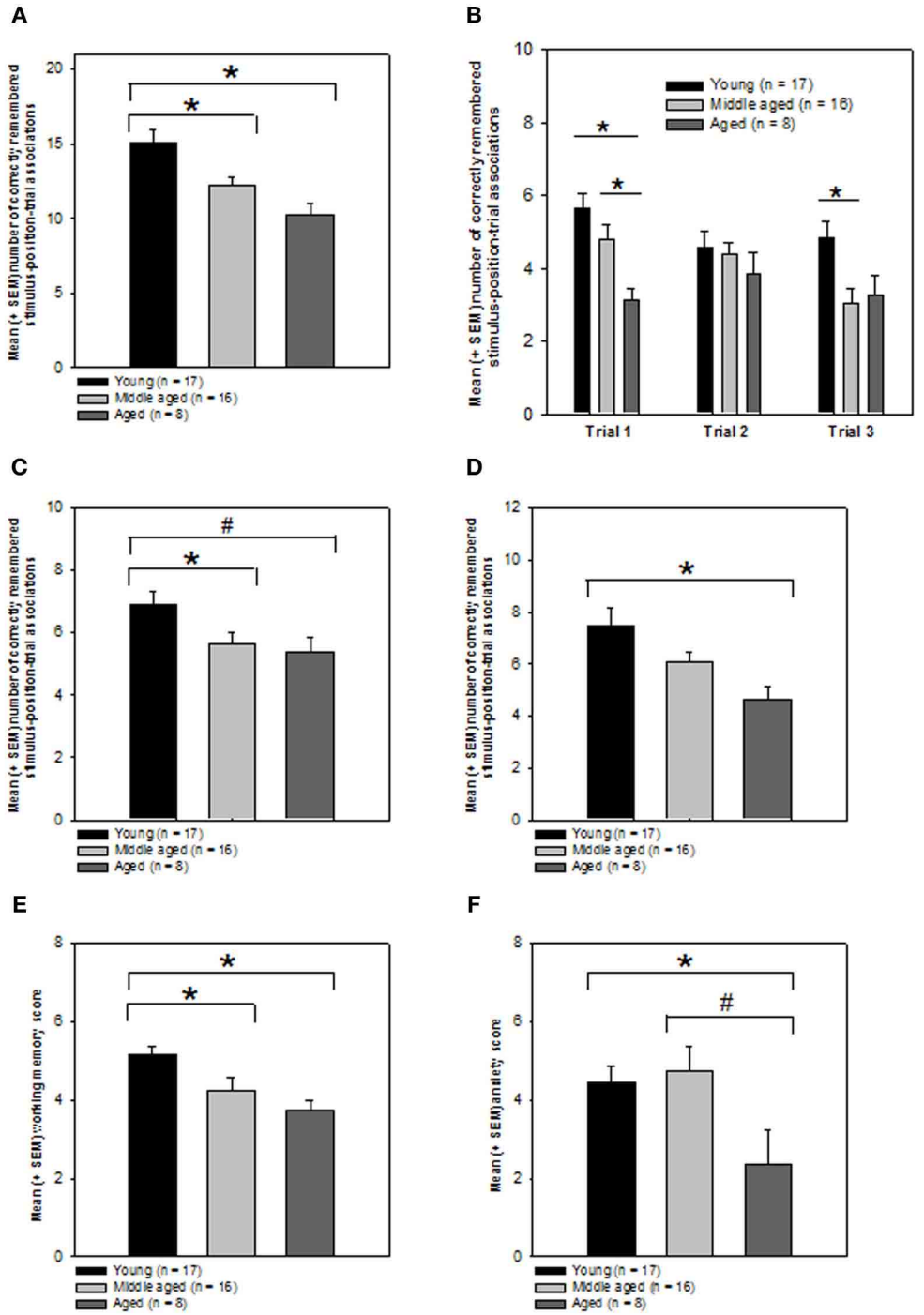


FIGURE 4 | Effects of aging on episodic memory performance, working memory, and emotionality. (A) Total episodic memory score. Bars represent mean and SEM number of correctly remembered stimulus-position-trial associations for indicated groups. $^{*}P \leq 0.05$, Holm–Sidak test. **(B)** Performance on individual presentation trials. Bars represent mean and SEM number of correctly remembered stimulus-position associations for indicated trials. $^{*}P \leq 0.05$, Holm–Sidak test. **(C)** Context story relevant stimulus-position-trial performance. Bars represent mean and SEM total number of correctly remembered human-position-trial associations for indicated groups. $^{*}P \leq 0.05$, $^{\#}0.05 < P < 0.1$, Mann–Whitney rank sum test. **(D)** Context story non-relevant stimulus-position-trial performance. Bars represent mean and SEM total number of correctly remembered pigeon-position-trial associations for indicated groups. $^{*}P \leq 0.05$, Holm–Sidak test. **(E)** Working memory performance. Bars represent mean and SEM working memory scores for indicated groups. $^{*}P \leq 0.05$, Mann–Whitney rank sum test. **(F)** Trait anxiety. Bars represent mean and SEM Goldberg anxiety scale scores. $^{*}P \leq 0.05$, $^{\#}0.05 < P < 0.1$, Student *t*-tests. Graphical presentation of the data: all data obtained with the episodic memory test and the neuropsychological tests were graphically presented as means ± SEM.

of $P = 0.017$) and middle-aged group ($T = 2.489$; $P = 0.0173$, significant at the critical P-level of $P = 0.025$). No significant difference was obtained for the comparison between the young and middle-aged group ($P > 0.05$).

While no significant difference between the groups was evident for the stimulus-position associations established on trial 2 (Kolmogorov–Smirnov test: $P > 0.05$, Levene test $P < 0.05$; Kruskal–Wallis One-Way analysis of variance on ranks: $P > 0.05$; **Figure 4B**), the groups performed significantly different when probed for the stimulus-position associations generated on trial 3 (Kolmogorov–Smirnov test: $P > 0.05$; Levene test: $P > 0.05$; ANOVA: $F_{(2,\ 38)} = 4.863$, $P = 0.013$).

The pair-wise *post-hoc* Holm–Sidak tests indicated a significant difference between the young and middle-aged group ($T = 2.933$; $P = 0.0057$, significant at the critical P-level of $P = 0.017$) but not for the remaining 2 comparisons (Ps > 0.05).

This result suggests that age-related changes in episodic memory performance are reflected by trial 1 and 3 performance. The inability of the second trial to discriminate between the groups might be due to processes of pro- and retroactive interference where the sequential acquisition of learning material has a detrimental effect on the subsequent retrieval process (Brophy et al., 2009). The susceptibility to pro- and retroactive interference might be possibly age-independent.

Episodic memory for context-story relevant vs. non-relevant stimuli

Next we analyzed whether the groups might show significant differences in the ability to establish and remember human-position-trial or pigeon-position-trial associations. We expected that the groups would differ significantly for the human context-relevant stimuli but possibly not for the context non-relevant pigeon stimuli.

A One-Way ANOVA on ranks revealed a trend toward a significant difference between the 3 groups regarding the human-position-trial associations (Kolmogorov–Smirnov test: $P > 0.05$, Levene test: $P < 0.05$; Kruskal–Wallis One-Way analysis of variance on ranks: $H = 5.345$, degrees of freedom: 2, $P = 0.069$, **Figure 4C**). Mann–Whitney rank sum tests for pair-wise comparisons revealed that the young group remembered the human-position-trial combinations significantly better as compared to the middle ($T = 216.5$, $P = 0.047$) group, while there was only a trend for a difference between the young and the aged group ($T = 74.5$, $P = 0.091$). The middle and aged groups performed not significantly different from each other ($P > 0.05$).

Contrarily to our hypothesis, the groups also differed significantly regarding their ability to remember the context-story non-relevant pigeon-position-trial combinations (Kolmogorov–Smirnov test: $P > 0.05$; Levene test $P > 0.05$, ANOVA: $F_{(2,\ 38)} = 4.986$, $P = 0.012$, **Figure 4D**). Pair-wise *post-hoc* Holm–Sidak tests for the pigeon-position-trial associations showed that the aged group remembered a significantly fewer number of pigeon-position-trial associations relative to the young group ($T = 3.075$; $P = 0.00389$, significant at the critical P-level of $P = 0.017$). There was no significant difference between the young and middle-aged group ($P > 0.05$) or the middle-aged and aged group ($P > 0.05$). Although statistically not significant, the aged group showed slightly better memory performances in the human-position-trial associations compared to the pigeon-position trial condition.

WITHIN-GROUP COMPARISONS OF THE EPISODIC MEMORY FOR CONTEXT-STORY RELEVANT vs. NON-RELEVANT STIMULI

Next we analyzed whether the performance of single groups was significantly different for human vs. pigeon-position-trial associations. However, none of the 3 groups showed a significant difference between the episodic memory for context-story relevant stimuli in comparison to the non-relevant stimuli (all Ps > 0.05).

NEUROPSYCHOLOGICAL AND PSYCHOLOGICAL ASSESSMENT

Working memory

In order to know whether the expected aging-related differences in episodic memory performance are at least in part due to changes in working memory performance we also measured this capacity in the three groups. A One-Way ANOVA on ranks revealed that the working memory performance of the 3 groups was indeed significantly different from each other (Kolmogorov–Smirnov test: $P < 0.05$; Levene test: $P > 0.05$; Kruskal–Wallis One-Way analysis of variance on ranks: $H = 13.997$, degrees of freedom: 2, $P < 0.001$, **Figure 4E**). In order to know which groups performed significantly different from each other, we computed Mann–Whitney rank sum tests for pair-wise comparisons. We found that the young group had significantly higher working memory scores as compared to both the middle ($T = 197.5$, $P = 0.008$) and aged groups ($T = 48$, $P = 0.001$). The latter two groups performed not significantly different from each other ($P > 0.05$).

Depressive symptoms

It is known that the incidence of major depression is increased in aged individuals and that depressive episodes are associated with memory impairments. We therefore tested whether possible differences in episodic memory performance between the 3 groups might be explained by differences in depressive symptoms. There were no significant differences between the groups on the Goldberg depression scale ($P > 0.05$).

Anxiety

We have hypothesized that age-related decline in episodic memory performance might be related to hypo-emotionality or changes in the processing of emotionally-valenced stimuli. Therefore, we also tested whether possible group-differences in episodic memory performance might be explained by differences in trait or state (experimental context-induced) anxiety.

Trait anxiety

A One-Way ANOVA indicated a trend for a difference between the groups in the Goldberg scale subtest measuring trait anxiety (Kolmogorov–Smirnov test: $P > 0.05$, Levene test $P > 0.05$;

ANOVA: $F_{(2,\ 37)} = 2.781$, $P = 0.075$, **Figure 4F**). Pair-wise comparisons by means of Student *t*-tests revealed that the aged group showed significantly lower trait anxiety scores as compared to the young group (Kolmogorov–Smirnov test: $P > 0.05$, Levene test $P > 0.05$; $T = 2.236$, degrees of freedom: 22, $P = 0.036$), but only a trend for a difference as compared to the middle-aged group (Kolmogorov–Smirnov test: $P > 0.05$, Levene test $P > 0.05$; $T = 2.016$, degrees of freedom: 22, $P = 0.056$). No significant difference was found for the comparison between the young and middle-aged group ($P > 0.05$).

State anxiety

The comparison of the STAI state anxiety reference values reported for patients with phobia or anxiety disorders (*F*40/*F*41) mean: 42.7 ± 11.5 (Laux et al., 1981) with the mean scores of our 3 age groups: young: 50.59 ± 0.68, middle aged: 52.25 ± and aged: 51.0 ± 2.67 indicates that the context story in combination with the slide presentations has induced an level of emotional arousal in the participants that is similar to the one that has been measured in clinical populations. However, there was no significant difference between groups in the state anxiety test ($P > 0.05$). This result suggest that the experimental context induced similar levels of emotional activation respectively anxiety in the 3 groups.

Correlations

We also performed Pearson and Spearman rank correlations including data from all participants between different measures of episodic memory performance and state and trait anxiety scores. There was only one significant correlation between the state anxiety scores and the episodic memory scores for the pigeon-position-trial associations ($R_{(38)} = 0.322$, $P = 0.049$) all other correlations obtained failed to reach the level of statistical significance. We also calculated single group correlations for the significant correlation found between state anxiety and pigeon-position-trial associations, but did not found significant correlations between the two variables in any group (all *P*s > 0.05). The highest correlation found was $R_{(16)} = 0.431$ with a *P*-value of 0.095 in the middle aged group.

DISCUSSION

SUMMARY

In the present study, we hypothesized that episodic memory deficits will be associated with changes in trait and/or state anxiety in the aged but also in the middle-aged group. The results presented above suggest that our novel test of episodic memory that measures the core components of an episodic memory (event, spatial, and temporal information) and in addition probes the ability to form new episodic memories is suited to detect age-related impairments in episodic memory performance. The episodic memory deficits observed in the aged group were observed along with lower anxiety scores measured with the Goldberg anxiety scale. However, no significant correlation between episodic memory and trait or state anxiety scores were found.

EPISODIC MEMORY PERFORMANCE ON INDIVIDUAL PRESENTATION TRIALS

It is well known that aging affects episodic memory function more severely than other types of memory including semantic memory (Levine et al., 2002). It has been proposed that this difference is possibly mediated by changes in the processing of emotionally-competent stimuli (Allen et al., 2005; Kensinger, 2009). We found that the young group was able to remember a higher number of stimulus-position-trial associations (out of 27 associations to be remembered) as compared to both the middle-aged and aged groups. Age-dependent effects were most prominent when the recall of the information for trial 1 was tested. Here, the aged group performed inferior to both the young and middle-aged groups. These results suggest that the aged group failed to consolidate the trial 1 information (that had been acquired more than 2 h before the test) into long-term memory.

CONTEXT STORY RELEVANT AND NON-RELEVANT STIMULUS-POSITION-TRIAL PERFORMANCE

We hypothesized that context story-relevant stimuli (men and woman) might be generally better remembered as context story non-relevant stimuli and therefore would be much better suited to identify age-dependent impairments in episodic memory performance. However, the present results suggest that this was not the case. In fact there was no significant difference between the memory of the context story-relevant vs. non-relevant stimuli even in the young group. We found that both types of stimuli were suited to detect age-dependent changes in episodic memory performance. As expected the young group showed better performance for context story-relevant stimuli as compared to the other groups. Interestingly, the aged group showed impaired context story non-relevant recall of pigeon-position-trial associations as compared to the young group. The aged group also showed slightly better (although statistically not significant) memory performance in the context-story relevant human-position-trial associations condition as compared to the pigeon-position-trial associations condition. These results suggest the presence of an impairment in the possibly incidental or non-intentional encoding of information that is not directly relevant to the context-story in the aged group (Naveh-Benjamin et al., 2009). It seems that the limited attention and memory capacities of aged individuals do not permit the allocation of additional processing resources to attend to and encode context-story non-relevant stimuli. Another possible explanation of this deficit might be that the episodic memories encoded by aged individuals generally contain less event details and context-specific information. In fact there is evidence for limited information processing capacities in aged individuals as well as changes in the management and allocation of processing resources in learning situations (Craik and Byrd, 1982).

Interestingly we found a significant correlation between the state anxiety scores and the episodic memory scores for the pigeon-position-trial associations. Given that the old group showed lower trait anxiety scores and impaired episodic memory for pigeon-position-trial associations, it is tempting to speculate that incidental or non-intentional encoding of context-story non-relevant information depends on the level of trait anxiety.

AGING-DEPENDENT EFFECTS OF WORKING MEMORY ON THE ENCODING OF EPISODIC INFORMATION

It is known that working memory mediated by the dorsolateral prefrontal cortex plays a role in the encoding and retrieval of long-term memories including episodic memory (Lee et al., 2000; Cabeza et al., 2002; Blumenfeld and Ranganath, 2006). Thus, we also investigated whether age-related differences in episodic memory performance might be explained by changes in working memory performance. We found that working memory performance is impaired in the middle-aged and aged groups as compared to the young group. It is possible that these working memory deficits might be related to an impairment at the encoding stage of episodic memory formation (Unsworth et al., 2011) in the middle-aged and aged groups in the course of the presentation of the 3 trials.

DEPRESSIVE SYMPTOMS AND EPISODIC MEMORY

It is known that the incidence of depressive symptoms that also include episodic memory impairments are increased in the aged population (Airaksinen et al., 2004, 2007; Potter and Steffens, 2007). In geriatric settings cognitive symptoms that are associated with a depressive disorder are often misinterpreted as dementia (Ouldred and Bryant, 2008). Therefore, we tested whether the middle-aged and aged group might exhibit an increase in depressive symptoms. However, this was not the case so that the differences in episodic memory performance observed between the young and the older groups are unlikely to be due to a depressive condition in the middle-aged and/or aged group.

AGING-RELATED IMPAIRMENTS IN EPISODIC MEMORY AND CHANGES IN EMOTIONALITY

It is well known that emotionally arousing events are more likely to be encoded into long-term memory as compared to neutral events (Cahill and McGaugh, 1998). Furthermore, it has been hypothesized that emotional activation might be a prerequisite for episodic memory formation (Dere et al., 2010). In the present study, we asked whether aging-related episodic memory decline might be associated with changes in state or trait anxiety. Trait anxiety reflects a general personality trait to exhibit anxiety-related behavior at the cognitive (e.g., worrying) and/or behavioral level (e.g., avoidance of anticipated fear-inducing situations) that might be affected by aging. Trait anxiety is relatively stable across time while state anxiety shows large fluctuations and depends on the current context.

We found lower anxiety scores in the aged group as compared to the young and middle-aged group. This change in the trait anxiety levels in the aged group might be associated with a reduced emotional activation by the experimental situation or by the context story. Given that there were no significant correlations between total episodic memory and trait or state anxiety scores, it still remains to be determined whether this difference in anxiety is indeed related to the impaired episodic memory performance in the aged group. In future studies, we will measure physiological correlates of emotional activation such as the blood pressure and the galvanic skin reaction in the aged population to test the above proposed relationship between decreased anxiety and impairments in episodic memory in healthy aged individuals.

There is evidence that older individuals exhibit a decreased functional connectivity between the amygdala and the hippocampus (St Jacques et al., 2009). Episodic memory impairments in the elderly might be related to a diminished emotional modulation of declarative memory formation implemented by the amygdala-hippocampus axis (McGaugh et al., 1996; Tulving and Markowitsch, 1998; Dere et al., 2010). This hypothesis might be tested by combining our novel test of episodic memory with hippocampal-amygdala EEG coherence measurements and neuroimaging methods such as functional MRI.

Novel tests of episodic memory and limitations of the present task

Recently novel episodic memory tasks have been designed that are based on paradigms that have been originally developed to study episodic-like memory in animals (Clayton and Dickinson, 1999; Dere et al., 2005a). These tasks are either based on the "what, where, and when" (Pause et al., 2010; Holland and Smulders, 2011) or "what, where, which" (Easton et al., 2012) principles. Pause et al. (2010) followed a reverse translational approach and adapted the episodic-like memory test for rodents (Dere et al., 2005a) to humans and devised a computer-based test. However, this test requiring the active exploration of the computer screen using a keyboard might be too complicated to be run with older individuals. Others have probed episodic memory based on the "what, where, and when" paradigm by asking participants to hide different coin types (what) in different locations (where) on two separate occasions (when) (Holland and Smulders, 2011). These authors conclude that paradigms based on the "what, where, and when" paradigm might be indeed reliable tests of episodic memory function. Another approach to translate findings from animal research into tests of human episodic memory was based on the "what, where, and which" paradigm (Easton et al., 2012). Here, it has been proposed that tasks using contextual information to discriminate events could only be accurately performed using recollection, not familiarity, while tasks using temporal information to discriminate events might be solved using either recollection or familiarity (Easton et al., 2012). It thus remains to be determined whether tasks based on the "what, where, and when" paradigm rely more on recollection vs. familiarity-based memory performance.

In order to fully explore the strengths and limits of the novel episodic memory test described here, follow-up studies should be performed in which recollection vs. familiarity-based memory performance is assessed, sample sizes are increased and in which direct physiological measurements of emotional activation during task performance are correlated with the episodic memory scores obtained.

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REFERENCES

Airaksinen, E., Larsson, M., Lundberg, I., and Forsell, Y. (2004). Cognitive functions in depressive disorders: evidence from a population-based study. *Psychol. Med.* 34, 83–91.

Airaksinen, E., Wahlin, A., Forsell, Y., and Larsson, M. (2007). Low episodic memory performance as a premorbid marker of depression: evidence from a 3-year follow-up. *Acta Psychiatr. Scand.* 115, 458–465.

Allen, P. A., Kaut, K. P., Lord, R. G., Hall, R. J., Grabbe, J. W., and Bowie, T. (2005). An emotional mediation theory of differential age effects in episodic and semantic memories. *Exp. Aging Res.* 31, 355–391.

Blumenfeld, R. S., and Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J. Neurosci.* 26, 916–925.

Bornstein, R., Baker, G., and Douglass, A. (1991). Depression andmemoryin major depression disorder. *J. Neuropsychiatry Clin. Neurosci.* 3, 78–80.

Brophy, L. M., Jackson, M., and Crowe, S. F. (2009). Interference effects on commonly used memory tasks. *Arch. Clin. Neuropsychol.* 24, 105–112.

Burgess, N., Maguire, E. A., and O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron* 35, 625–641.

Cabeza, R., Dolcos, F., Graham, R., and Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage* 16, 317–330.

Cahill, L., and McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* 21, 294–299.

Clayton, N. S., and Dickinson, A. (1999). Episodic-like memory during cache recovery by scrub jays. *Nature* 395, 272–274.

Craik, F. I. M., and Byrd, M. (1982). *Aging and Cognitive Deficits: The Role of Attentional Processes*. New York, NY: Plenum Press.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2005a). Integrated memory for objects, places and temporal order: evidence for episodic-like memory in mice. *Neurobiol. Learn. Mem.* 84, 214–221.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2005b). Protocol: episodic-like memory in mice: simultaneous assessment of object, place and temporal order memory. *Brain Res. Brain Res. Protoc.* 16, 10–19.

Dere, E., Pause, B., and Pietrowsky, R. (2010). Emotion and episodic memory in neuropsychiatric disorders. *Behav. Brain Res.* 215, 162–171.

Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 6, 734–746.

Easton, A., Webster, L. A., and Eacott, M. J. (2012). The episodic nature of episodic-like memories. *Learn. Mem.* 19, 146–150.

Goldberg, D., Bridges, K., Duncan-Jones, P., and Grayson, D. (1988). Detecting anxiety and depression in general medical settings. *BMJ* 297, 897–899.

Holland, S. M., and Smulders, T. V. (2011). Do humans use episodic memory to solve a What-Where-When memory task? *Anim. Cogn.* 14, 95–102.

Kart-Teke, E., De Souza Silva, M. A., Huston, J. P., and Dere, E. (2006). Wistar rats show episodic-like memory for unique experiences. *Neurobiol. Learn. Mem.* 85, 173–182.

Kaszniak, A. W., and Menchola, M. (2012). Behavioral neuroscience of emotion in aging. *Curr. Top. Behav. Neurosci.* 10, 51–66.

Kensinger, E. A. (2009). How emotion affects older adults' memories for event details. *Memory* 17, 208–219.

Kensinger, E. A., Addis, D. R., and Atapattu, R. K. (2011). Amygdala activity at encoding corresponds with memory vividness and with memory for select episodic details. *Neuropsychologia* 49, 663–673.

Kirchhoff, B. A., Wagner, A. D., Maril, A., and Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J. Neurosci.* 20, 6173–6180.

Laux, L., Glanzmann, P., Schaffner, P., and Spielberger, C. D. (1981). *Das State-Trait-Angstinventar. Theoretische Grundlagen und Handanweisung*. Weinheim: Beltz Test GmbH.

LeDoux, J. (2007). The amygdala. *Curr. Biol.* 17, R868–R874.

Lee, A. C., Robbins, T. W., and Owen, A. M. (2000). Episodic memory meets working memory in the frontal lobe: functional neuroimaging studies of encoding and retrieval. *Crit. Rev. Neurobiol.* 14, 165–197.

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval, *Psychol. Aging* 17, 677–689.

Libkuman, T. M., Stabler, C. L., and Otani, H. (2004). Arousal, valence, and memory for detail. *Memory* 12, 237–247.

Markowitsch, H. J., and Staniloiu, A. (2011). Amygdala in action: relaying biological and social significance to autobiographical memory. *Neuropsychologia* 49, 718–733.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* 27, 1–28.

McGaugh, J. L., Cahill, L., and Roozendaal, B. (1996). Involvement of the amygdala in memory storage: interaction with other brain systems. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13508–13514.

McIntyre, C. K., Power, A. E., Roozendaal, B., and McGaugh, J. L. (2003). Role of the basolateral amygdala in memory consolidation. *Ann. N.Y. Acad. Sci.* 985, 273–293.

Nashiro, K., and Mather, M. (2011). How arousal affects younger and older adults' memory binding. *Exp. Aging Res.* 37, 108–128.

Naveh-Benjamin, M., Shing, Y. L., Kilb, A., Werkle-Bergner, M., Lindenberger, U., and Li, S. C. (2009). Adult age differences in memory for name-face associations: the effects of intentional and incidental learning. *Memory* 17, 220–232.

Nebes, R. D., Butters, M. A., Mulsant, B. H., Pollock, B. G., Zmuda, M. D., Houck, P. R., et al. (2000). Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol. Med.* 30, 679–691.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., and Bäckman, L. (2012). Memory aging and brain maintenance. *Trends Cogn. Sci.* 16, 292–305.

Nyberg, L., McIntosh, A. R., Houle, S., Nilsson, L. G., and Tulving, E. (1996). Activation of medial temporal structures during episodic memory retrieval. *Nature* 380, 715–717.

Ouldred, E., and Bryant, C. (2008). Dementia care. Part 1: guidance and the assessment process. *Br. J. Nurs.* 17, 138–145.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., and Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320.

Pause, B., Jungbluth, C., Adolph, D., Pietrowsky, R., and Dere, E. (2010). Induction and measurement of episodic memories in healthy adults. *J. Neurosci. Methods* 189, 88–96.

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M., et al. (2006). Structure-function correlates of cognitive decline in aging. *Cereb. Cortex* 16, 907–915.

Potter, G. G., and Steffens, D. C. (2007). Contribution of depression to cognitive impairment and dementia in older adults. *Neurologist* 13, 105–117.

Rajah, M. N., Kromas, M., Han, J. E., and Pruessner, J. C. (2010). Group differences in anterior hippocampal volume and in the retrieval of spatial and temporal context memory in healthy young versus older adults. *Neuropsychologia* 48, 4020–4030.

Rönnlund, M., Nyberg, L., Bäckman, L., and Nilsson, L. G. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychol. Aging* 20, 3–18.

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S. C., and Lindenberger, U. (2010). Episodic memory across the lifespan: the contributions of associative and strategic components. *Neurosci. Biobehav. Rev.* 34, 1080–1091.

Spielberger, C. D., Gorsuch, R. L., and Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

St Jacques, P. L., Dolcos, F., and Cabeza, R. (2009). Effects of aging on functional connectivity of the amygdala for subsequent memory of negative pictures: a network analysis of functional magnetic resonance imaging data. *Psychol. Sci.* 20, 74–84.

Tsivilis, D., Vann, S. D., Denby, C., Roberts, N., Mayes, A. R., Montaldi, D., et al. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nat. Neurosci.* 11, 834–842.

Tulving, E. (1983). *Elements of Episodic Memory*. London: Oxford University Press.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25.

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204.

Unsworth, N., Brewer, G. A., and Spillers, G. J. (2011). Variation in working memory capacity and episodic memory: examining the

importance of encoding specificity. *Psychon. Bull. Rev.* 18, 1113–1118.
Van Petten, C., Plante, E., Davidson, P. S., Kuo, T. Y., Bajuscak, L., and Glisky, E. L. (2004). Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia* 42, 1313–1335.
Wheeler, M. A., Stuss, D. T., and Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychol. Bull.* 121, 331–354.
Williams-Gray, C. H., Foltynie, T., Lewis, S. J., and Barker, R. A. (2006). Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options. *CNS Drugs* 20, 477–505.
Wolf, O. T. (2012). Immediate recall influences the effects of pre-encoding stress on emotional episodic long-term memory consolidation in healthy young men. *Stress* 15, 272–280.
Wolff, M., Loukavenko, E. A., Will, B. E., and Dalrymple-Alford, J. C. (2008). The extended hippocampal-diencephalic memory system: enriched housing promotes recovery of the flexible use of spatial representations after anterior thalamic lesions. *Hippocampus* 18, 996–1007.

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The cognitive aging of episodic memory: a view based on the event-related brain potential

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A cardinal feature of older-adult cognition is a decline, relative to the young, in the encoding and retrieval of personally relevant events, i.e., episodic memory (EM). A consensus holds that familiarity, a relatively automatic feeling of knowing that can support recognition-memory judgments, is preserved with aging. By contrast, recollection, which requires the effortful, strategic recovery of contextual detail, declines as we age. Over the last decade, event-related brain potential (ERPs) have become increasingly important tools in the study of the aging of EM, because a few, well-researched EM effects have been associated with the cognitive processes thought to underlie successful EM performance. EM effects are operationalized by subtracting the ERPs elicited by correctly rejected, new items from those to correctly recognized, old items. Although highly controversial, the mid-frontal effect (a positive component between ∼300 and 500 ms, maximal at fronto-central scalp sites) is thought to reflect familiarity-based recognition. A positivity between ∼500 and 800 ms, maximal at left-parietal scalp, has been labeled the left-parietal EM effect. A wealth of evidence suggests that this brain activity reflects recollection-based retrieval. Here, I review the ERP evidence in support of the hypothesis that familiarity is maintained while recollection is compromised in older relative to young adults. I consider the possibility that the inconsistency in findings may be due to individual differences in performance, executive function, and quality of life indices, such as socio-economic status.

Keywords: cognitive aging, episodic memory, familiarity, recollection, ERPs

INTRODUCTION

A great deal of experimental evidence indicates that older, relative to younger, adults exhibit a decline in episodic memory (EM) function, i.e., in the encoding and retrieval of personally relevant events (Light, 1991; Rugg and Morcom, 2005; Friedman et al., 2007; McDaniel et al., 2008). Over the last decade, the scalp-recorded event-related brain potential (ERP) has become an increasingly important tool in the study of the aging of EM for two reasons. First, ERPs have exquisite temporal resolution, in the millisecond range, and can, therefore, track the processing of mnemonic information at the speed with which those events transpire within the brain. Second, a few, well-researched ERP, EM effects have been associated with the cognitive processes thought to underlie successful recognition-memory performance (e.g., Yonelinas, 2002).

For example, Old/New recognition-memory tasks include a study phase followed by a delay, after which a recognition test is administered. Participants have to respond to a randomly intermixed series of previously studied (i.e., old) and unstudied (new) items, typically by quickly and accurately pressing a response button concordant with the old/new status of the item. At least two sets of processes are thought to contribute to performance on this type of recognition-memory task: familiarity and recollection. They have a long history of study in cognitive psychology (Mandler, 1980) as well as cognitive neuroscience (Yonelinas, 2002) and have played important roles in understanding age-related changes in EM (Jennings and Jacoby, 1993). Familiarity is thought to be fast acting and relatively automatic, with the majority of studies suggesting comparative preservation with aging (Howard et al., 2006). However, recent ERP (Duarte et al., 2006; Wang et al., 2012) and behavioral (Prull et al., 2006; but see Koen and Yonelinas, 2013 below) findings suggest that this might not always be the case. By contrast with familiarity, recollection takes longer to evolve, is deliberate and, therefore, thought to involve executive control. In behavioral studies, older, relative to young, adults consistently exhibit deficits in recollection-based processes (Jennings and Jacoby, 1993; Howard et al., 2006), possibly because they are impaired on tasks that tap executive-control functions (Braver and Barch, 2002; Buckner, 2004; but see Verhaeghen, 2011). In a very recent meta-analysis, Koen and Yonelinas (2013) came to the similar conclusion that, whereas recollection showed large decrements with aging, familiarity demonstrated small, though significant, reductions. In a follow-up experiment with participants between the ages of 40 and 81, these same investigators (Koen and Yonelinas, 2013) used several methods to estimate familiarity and recollection. Again, recollection-based processing showed large declines with aging, whereas familiarity-based processing was preserved, with each estimating procedure yielding the same pattern of findings. The fact that all methods employed produced the same result is strong evidence for the hypothesis that recollection shows clear and consistent declines with aging, while familiarity, if reduced at all, exhibits a much smaller diminution and is more often preserved with aging.

A good example of the two sets of mnemonic processes is demonstrated by the following scenario that we all have experienced at one time or another: you see a face in the crowd and have an immediate "aha" response that you know this person (familiarity-based judgment; i.e., a feeling of knowing), but cannot immediately bring to mind, for instance, the person's name, in what type of venue you met the person and his or her occupation (recollection of some of the previous episode's contextual details). The recovery of that kind of contextual information may take several hundred milliseconds or even longer. Such differential timing of familiarity- and recollection-based processes cannot be easily studied with fMRI techniques because the hemodynamic response is quite sluggish and cannot resolve processes occurring within milliseconds of stimulus presentation.

However, recognition-memory processes have been well studied with ERP methods (Johnson, 1995; Friedman and Johnson, 2000; Mecklinger, 2000; Paller, 2004; Rugg and Curran, 2007). Familiarity- and recollection-based EM effects are operationalized by subtracting the ERPs elicited by correctly rejected new items (CRs) from those to correctly recognized, old items (Hits). It is important to note that the *difference* between these two ERPs presumably reflects EM retrieval phenomena, and it is the difference between old and new ERPs that is the critical measure in most of these investigations. Although decidedly controversial, the mid-frontal EM effect (also known as the FN400; Curran, 2000) is a positive component between ∼300 and 500 ms, maximal at fronto-central scalp sites, and thought by some to reflect familiarity-based recognition (see below for a description of the controversy). A subsequent positivity between ∼500 and 800 ms, maximal at left-parietal scalp, has been labeled the left-parietal EM effect. A great deal of data accrued over the last 20 years and a rather strong consensus suggest that this brain activity reflects recollection-based retrieval (Rugg and Curran, 2007). A third, positive EM effect that generally occurs during and/or following the diminution of the left-parietal EM effect and endures for several hundred milliseconds, has been associated with the evaluation and monitoring of the products of a retrieval attempt. This activity is focused over right-frontal scalp, has been linked to executive function and the prefrontal cortex, but may not reflect mnemonic processes *per se* (Hayama et al., 2008). It has been labeled the right-frontal EM effect (Friedman and Johnson, 2000). Because of space limitations, this review will consider only the first two EM effects, those that have been the most frequent subjects of study (for a review of ERP activity related to executive-control processes at retrieval, see Mecklinger, 2010).

Figure 1 depicts the ERPs associated with correctly recognized old items (Hits) and CRs in young adults and displays the two phenomena of interest. The mid-frontal and left-parietal EM effects are identified and the typical latency windows used to measure them are shaded (mid-frontal = dark gray; left-parietal = light gray). The reduction with repetition (i.e., an increment in positive amplitude) in the frontally oriented N400 can be clearly observed over frontal scalp. The functional significance of the difference between old and new ERPs in this region (usually measured between 300 and 500 ms) has been linked with familiarity but, as noted earlier, this interpretation is hotly debated. The subsequent enhancement in positivity (500–800 ms) to old compared to new items over left-parietal scalp can also be observed clearly. As noted, this EM effect has been associated with recollection.

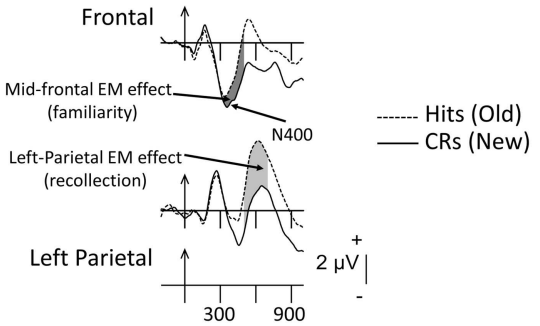


FIGURE 1 | Grand-mean ERPs averaged across 16 young adults to correctly recognized old items (Hits, dashed lines) and correctly rejected new items (CRs, solid lines). Arrows mark stimulus onset with vertical-hash, timing marks every 300 ms. Dark-gray shading in the waveforms indicates the mid-frontal effect (300–500 ms); light-gray shading reflects the left-parietal effect (500–800 ms).

The association between the mid-frontal EM effect and familiarity is based upon findings that its amplitude (1) is similar to hits regardless of whether they are endorsed with remember (R; recollection) or know (K; familiarity) judgments (Trott et al., 1999); (2) is similar to hits regardless of whether the contextual details from the previous experience are correctly identified (Friedman, 2004); (3) is similar to hits and falsely recognized items that are highly similar to previously studied old items, i.e., "lures" (Curran, 2000; Nessler et al., 2001); and (4) shows a graded relation with memory strength (i.e., level of familiarity; Woodruff et al., 2006; Wang et al., 2012). The longer-latency parietal EM effect has been associated with recollection because its amplitude (1) is larger to hits associated with R relative to K judgments (Smith, 1993; Trott et al., 1999); (2) is larger to hits associated with correct compared to incorrect source judgments (Wilding and Rugg, 1996); (3) is larger to hits compared to falsely recognized, but very similar lure items (Curran, 2000); and (4) is larger the greater the amount of information retrieved about the previous episode (Wilding, 2000; Vilberg and Rugg, 2009). Consistent with the mid-frontal and parietal EM effects reflecting distinct mnemonic processes, they differ in timing and distribution of amplitudes across the scalp (i.e., topography), suggesting that these effects are undergirded by at least partially non-overlapping neural networks (Johnson et al., 1998; Rugg and Yonelinas, 2003; Friedman, 2004).

In the review that follows, I will cover those age-related investigations that have been published since my last relatively comprehensive evaluation of the literature (Friedman, 2000). Although my colleagues and I included some review material in a later publication (Friedman et al., 2007), that paper was not a thorough assessment of the age-related memory and ERP findings. I will not include encoding-related ERP data because there have not been a sufficient number of papers in this area to come to a clear conclusion, although the handful of papers that do exist suggest a deficit in encoding-related processes (Nessler et al., 2006; Friedman, 2007; see also Johnson et al., 2013). I will also not discuss

age-related studies of retrieval-cue processing (e.g., Morcom and Rugg, 2004), as these are outside the focus of this review. Similarly, continuous-recognition-memory (Walhovd et al., 2006), relative to Old/New paradigms, are known to depend upon distinctly different cognitive mechanisms (Friedman, 1990). Hence, these will also not be included.

I start with a brief description of the types of recognition-memory tasks that have been employed typically in studies of neurocognitive aging. Most ERP investigators of recognition-memory phenomena have used verbal items as to-be-remembered events. Hence, the possibility that the mid-frontal EM effect might reflect conceptual priming rather than familiarity cannot be ruled out definitively. Specifically, repeating a previously studied item during the recognition-memory test phase engenders a reduction of the N400 component (between ∼ 300 and 500 ms), which comprises one aspect of the mid-frontal EM effect (**Figure 1**). The N400 is associated strongly with semantic processing, i.e., it is conceptually based (Kutas and Hillyard, 1980). Moreover, some amnesic patients show deficits in familiarity-based processing during recognition-memory testing, while some of these same patients show intact conceptual priming (Olichney et al., 2000). Hence, because the vast majority of investigators of ERP memory-related phenomena have used words as memoranda, the processes involved in the conceptual priming shown by the amnesic patients and controls in the Olichney et al. (2000) experiment may overlap those reflected in the reduction of the N400 comprising one aspect of the mid-frontal EM effect. Therefore, rather than reflecting familiarity *per se*, the mid-frontal EM effect could be associated with conceptual priming. This is currently highly contentious (see Paller et al., 2012 and Mecklinger et al., 2012 for a thorough treatment of these competing positions).

All of the data reviewed below come from investigations of variants of the recognition-memory paradigm and are, therefore, thought to reflect EM processes. Hence, I will assume that, although familiarity and conceptual priming covary in most studies of recognition memory, the mid-frontal EM effect is a putative sign of familiarity-based processing. However, I will also attempt, in the summaries of each section, to determine whether conceptual priming could also have accounted for the results.

Additionally, some investigators (e.g., Nessler et al., 2007; Duverne et al., 2009), have interpreted their ERP data as indicative of "compensation," in which older adults show electrical activity over different scalp regions compared to their young-adult counterparts (for fMRI data, see review by Grady, 2012). Compensation refers to the possibility of neural plasticity in healthy older adults, in which they may be able to reorganize neural networks (not recruited by the young) in order to cope with increased task complexity in the face of the deleterious effects of aging on the brain. Whether this hypothesis can be supported by the available ERP data is a topic that I will consider at the end of this review.

Three types of recognition-memory tasks have been used – simple, Old/New recognition, a more complex version of the Old/New paradigm, labeled the Remember (R)/Know (K) paradigm (Tulving, 1985), and the "source" memory task (for descriptions, see immediately below). Cued-recall paradigms have also been used (e.g., Angel et al., 2009), and I will discuss those studies in a separate section. In each of these paradigms, both pictures and words have been presented as memoranda. Surface format of stimulus material might be important in determining whether familiarity- as well as recollection-based EM effects are observed, especially in older adults, because pictures provide a much richer array of perceptual detail and enhance semantic elaboration to a greater extent than words (Yonelinas, 2002). Hence, I will add this distinction to the summaries of each section of the review.

During the test phase in Old/New recognition, one has to respond simply by judging whether the current item (i.e., the copy cue) is old or new, usually via reaction time (RT). To perform adequately on this task, either familiarity or recollection (or both) can be instrumental in reaching a decision. By contrast, in the R/K task, participants respond R if an old item is associated with any contextual details, be they inherent in the stimulus (e.g., semantic associates that are retrieved during encoding) or thoughts or ideas the person had during the time the item was encoded. A participant indicates K, when the item has been on the study list, but no contextual details can be recovered. R judgments are generally thought to reflect recollection-based decisions, whereas K judgments are thought to indicate familiarity-based decisions. As noted, in the R/K paradigm a wide variety of contextual details can underlie an R judgment. By contrast, in source-memory tasks, experimentally created, "diagnostic," details or sources must be recovered during the test phase, although non-diagnostic details may also be retrieved. In these paradigms, recollection is thought to contribute more than familiarity, as it is believed that one must time travel back to the prior episode in order to recover the diagnostic, contextual information (this may also be true in the case of an R judgment). Both of these types of memory task might be considered "source" tasks, in which the nature of the sought-for information differs. Although this might seem obvious, mind-traveling back in time is most likely one of the reasons why recollection-based processes take longer to transpire than those involved in familiarity-based retrieval (McElree et al., 1999).

REVIEW OF STUDIES

When available, I have indicated the age range of young- and older-adult samples for each of the studies I review below. When ranges weren't available, I have inserted mean ages (±SD).

OLD/NEW RECOGNITION-MEMORY PARADIGMS

As noted earlier, two old minus new EM effects have been the most heavily researched – the mid-frontal and left-parietal. These are depicted from an investigation by Nessler et al. (2007), whose data can serve to summarize the age-related findings for putative recollection-based neural activity recorded during the test phases of Old/New recognition-memory paradigms. This is so because similar age-related differences in the magnitude of recollection-related electrical activity have been reported by several other investigators (reviewed below). The data in **Figure 2** were recorded from 16 young (18–29 years old) and 16 older adults (62–86) in a simple, Old/New recognition-memory paradigm. Participants viewed a list of words and then, following a 5-min delay, saw the same set of "old" words intermixed randomly with a set of new words. During the test phase, subjects were asked to judge whether the items were old or new via choice, speeded and accurate old/new button presses. **Figure 2** shows that both young and older adults

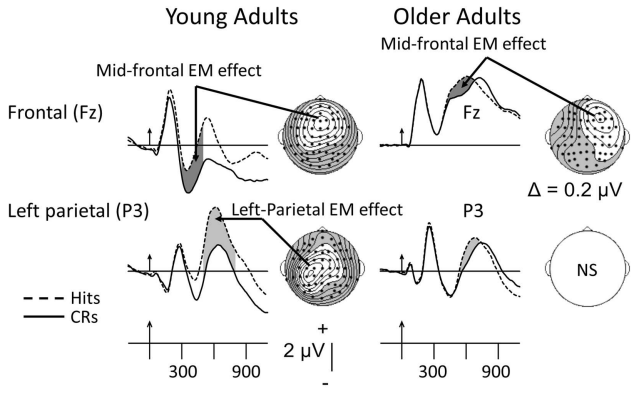


FIGURE 2 | Grand-mean ERPs averaged across 16 young and 16 older adults to correctly recognized old items (Hits, dashed lines) and correctly rejected new items (CRs, solid lines). Arrows mark stimulus onset with vertical-hash, timing marks every 300 ms. Dark-gray shading in the waveforms indicates the mid-frontal effect; light-gray shading reflects the left-parietal effect. NS, not significant. The maps here and in subsequent figures were computed by calculating contours using the spherical spline algorithm (Perrin et al., 1989) and data from all 62 electrodes (dots). In the topographic maps, unshaded regions reflect positivity; shaded regions reflect negativity. The data have been adapted from Nessler et al. (2007). The mid-frontal and left-parietal maps for the young were computed, respectively, between 300–500 and 500–800 ms. Due to latency prolongation in the older adults, the mid-frontal EM effect was computed between 400 and 600 ms.

exhibit intact and significant mid-frontal EM effects, putatively reflecting familiarity. By contrast, **Figure 2** shows that only the young adults display a reliable left-parietal EM effect, presumably reflecting recollection-based processes.

Wolk et al. (2009) also used a standard Old/New recognition task and found that young (18–30) relative to older (65–85), adults produced a greater magnitude recollection effect with words as stimuli. The mid-frontal effect was also reduced in the older-adult group. However, in similar fashion to Friedman et al., 2010; see Discussion below), when these investigators categorized their older adults into good and poor performers, only the old-high group showed neural evidence of recollection-based processing. Nonetheless, as in some of the other investigations described below, even the old-high, relative to the young-adult, recollection effect was still diminished in magnitude, suggesting that older adults recover less contextual information than their young-adult counterparts (Jacques St. and Levine, 2007).

Relative to words, pictorial stimuli are especially rich in perceptual detail and, hence, might be better recollected (i.e., the pictorial superiority effect) in both young and older adults. Nonetheless, although Gutchess et al. (2007) used full-color photographs of outdoor scenes as memoranda, their findings add to the evidence that older (61–74), relative to young (18–26), adults are impaired at recollection-based processing. Similar to the results of the Wolk et al. (2009) investigation, the mid-frontal EM effect was absent in the older-adult waveforms in the Gutchess et al. (2007) study. Ally et al. (2008b) compared directly, in young (18–25) and older (69–83) adults, picture–picture (study-test) with word–word recognition memory. Unlike the Gutchess et al. (2007) and Wolk et al. (2009) findings, the mid-frontal EM effect was of similar magnitude in young and older adults in the picture–picture condition, but was smaller in older, relative to young, adults in the word–word condition. Also in contrast to the results of Gutchess et al. (2007), Ally et al. (2008b) observed similar-magnitude recollection-based neural effects (and memory accuracies) in the picture–picture test condition in young and older adults, whereas in the word–word condition, young adults produced greater amplitudes (and memory accuracies) than older adults. Ally et al. (2008b) reported that there were no reliable topographic differences between young and older adults in the picture–picture condition. However, my visual impression was that older adults exhibited a strongly right-lateralized effect over frontal scalp (see also the section on Source-Memory and R/K Paradigms below), whereas the young adults showed the typical left-parietal scalp distribution associated with recollection.

In a follow-up investigation, Ally et al. (2008a) also employed pictures of common objects. During study, all objects were presented in canonical view. At test, all old items and an equal number of new items were presented for Old/New recognition testing. During the test phase, one-third of the old items were presented in the same canonical view as at study, one-third were rotated by 90°and one-third were presented in non-canonical views (see also Ranganath and Paller, 1999). Participants were to state "old" to studied items, regardless of the test object's viewpoint. Ally et al. (2008a) focused on the recollection-related effect and did not assess the mid-frontal EM effect. Their young-adult (18–25), recollection-based effect magnitudes (500–800 ms) were ordered as follows: canonical > rotated > non-canonical. This finding adds to the evidence that the parietal EM effect reflects recollection, because the match in retrieved information between the canonical copy cue and the study item is greater than that between the non-canonical copy cue and the study object. In accord with the ERP data, overall memory accuracy was better in the canonical than the rotated and non-canonical conditions and, relative to older adults (62–83), young adults' memory sensitivity was reliably better in all three conditions. Compared to the young, older adults demonstrated smaller parietal EM effects in all three conditions. However, older adults did not appear to produce significant recollection-based EM effects in any of the three conditions, consistent with the results of some of the studies reviewed earlier.

Like pictures, famous faces might also be expected to yield robust recollection-based processing to the extent that biographical features (i.e., the contextual details) are retrieved when the face is presented. Hence, Guillaume et al. (2009) used famous French faces as memoranda and assessed EM effects in young (25–30), middle-aged (50–64), and older adult (65–75) samples to determine when in the older age span declines in EM might begin. Although these authors collected R and K responses, they did not depict or analyze their data according to these judgments. The major findings were that (1) young, middle-, and older-aged participants showed similar memory accuracies; (2) the young and middle-aged groups both exhibited reliable mid-frontal EM effect effects, whereas the older adults did not; and (3) the young showed a reliable recollection-based EM effect, whereas the middle-aged sample's was marginal and the older-adults' effect was not significant. Unfortunately, there is some difficulty in assessing the

validity of these findings because, for both middle-aged and older-adults, there was a high degree of measurement overlap between the mid-frontal and left-parietal temporal intervals.

To summarize, with a wide variety of memoranda, the Old/New recognition-memory data reviewed above suggest that putative recollection-based processing (as reflected by the left-parietal EM effect; **Figure 2**) is reduced as healthy individuals grow older, with that decline possibly beginning in middle-age. However, because of the overlap in time windows in the Guillaume et al. (2009) study, this latter result may be questionable. The evidence as to whether older adults evince preservation of familiarity-based processing is equivocal, as there is inconsistency in the presence or absence of the putative familiarity effect in the waveforms of older adults, at least in the Old/New paradigms reviewed above. Furthermore, although the richness of perceptual details inherent in pictorial objects relative to words might be expected to elicit larger-magnitude familiarity- and/or recollection-based activities, the findings in older adults are too variable to support this distinction. Moreover, the results also do not appear to provide evidence, in any straightforward manner, for the interpretation that the mid-frontal effect can be explained by the conceptual priming between study and test items. For example, the differential effect of aging on the surface format of study-test pairings (i.e., picture–picture vs. word–word in Ally et al., 2008b), would be difficult to reconcile with a conceptual priming account of mid-frontal activity (see also Wang et al., 2012, below). Additionally, a recent review of the age-related status of conceptual priming concluded that this function was unaffected by aging (Fleischman, 2007). Hence, if the mid-frontal EM effect's magnitude were to change with aging, this would provide evidence against the view that this EM effect reflects conceptual priming. A further difficulty with more definitive interpretations of the EM effects recorded in canonical Old/New recognition paradigms is that behavioral proxies for familiarity and recollection have not typically been collected. This precludes the association of changes in magnitude and/or topography of a given EM effect with such proxy indices. This situation is remedied somewhat when source-memory and R/K investigations are considered.

SOURCE-MEMORY AND R/K PARADIGMS

Generally, older adults perform more poorly, relative to tests of "item" or content memory, on tests that necessitate the recovery of contextually based information (for review, see Spencer and Raz, 1995). This age-related finding is typical of all of the studies reviewed below. That is, when considering the accuracy data collapsed across source correct and incorrect judgments (i.e., Total Hits), older, relative to young, adults are not as impaired compared to when only correct-source judgments are considered. In the canonical ERP source-memory experiment, participants first produce an old/new, "item" judgment in response to the copy cue. Then, for any item judged to be "old," a short delay follows, after which an additional "source-memory" decision is given concerning which source (e.g., gender of voice; list membership; color of studied word/picture) the item was associated with during the encoding stage (e.g., Wegesin et al., 2002; Wilding and Rugg, 1996). It has been demonstrated that this "two-response" procedure generates highly similar ERP results as the one-response procedure, in which a Source 1, Source 2, or New judgment is made immediately following the presentation of the copy cue (Senkfor and Van Petten, 1998).

Unlike the picture from Old/New recognition tasks, the age-related pattern of findings is somewhat different when source-memory data are considered. The ERPs depicted in **Figure 3** provide an example of such data from a "two-response" procedure, in which participants first made an old/new judgment and then, for items judged old, generated a source decision (was the item presented in List 1 or List 2? see Wegesin et al., 2002, for complete details). The ERP data illustrated in **Figure 3** were recorded time-locked to the copy cue. Young adults (18–28) show the typical left-sided, posterior scalp distribution associated with recollection-based activity. By contrast, the older adults (60–80) exhibit a posterior-parietal topography, but it appears to be somewhat right-sided compared to that of the young (see also Duverne et al., 2009). This relatively anomalous distribution might well be due to the overlapping centrally oriented negativity that is prominent in the ERPs of the older adults (for other examples see Li et al., 2004, and Swick et al., 2006, and Discussion below). In the same time frame (1000–1100 ms), in the young-adult ERPs there is posterior-negative activity, but the most conspicuous feature of their distribution is the right-prefrontal EM effect thought to reflect post-retrieval monitoring and evaluation. In the Wegesin et al. (2002) study, the difference between young and older adults in parietal EM effect magnitude was not significant. Correspondingly, young and older adults displayed significant, similar-magnitude mid-frontal effects (data not shown). On the other hand, older adults exhibited a central negativity which was

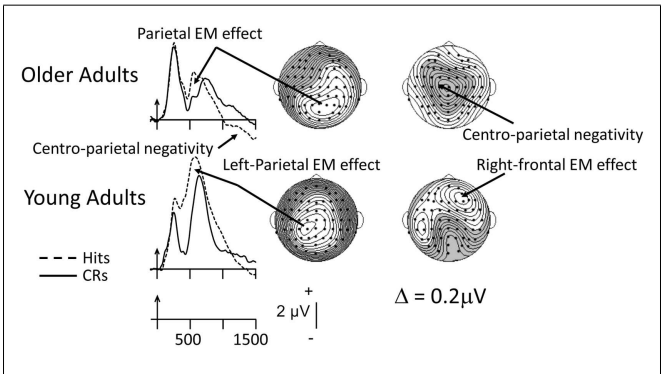


FIGURE 3 | Grand-mean ERPs averaged across 14 young and 14 older adults to correctly recognized old items (Hits; dashed lines) and correctly rejected new items (CRs, solid lines). Arrows mark stimulus onset, with time markers every 500 ms. The data were recorded during a source-memory paradigm in which two lists of sentences (i.e., the "sources," each with two nouns) had been presented (Wegesin et al., 2002). Participants had to decide whether the nouns were new or old and, for old items, which list the noun had come from. The ERPs are depicted at the left-parietal site where the parietal EM effect has been consistently identified (Friedman and Johnson, 2000). The waveforms associated with correctly recognized old items (Hits) have been averaged across the two nouns from each sentence and each list (or source). The topographic maps illustrating the parietal EM effects for young and older adults were based on a latency window from 500 to 600 ms; the latency window for the subsequent effects was based on a 1000–1100 ms time interval. The data have been adapted from Wegesin et al. (2002).

not present in the ERPs of the young. Wegesin et al. (2002) speculated that the central negativity in older adults may have reflected the re-representation of the nouns' visual images (Cycowicz et al., 2001), because several participants had used visualization strategies during encoding to memorize those stimuli. Wegesin et al. (2002) also suggested that this activity may have been "compensatory" because it was not present in the ERPs of the young. However, that argument does not rest on solid ground, as these authors did not attempt to relate the so-called compensatory activity to performance measures. I will come back to this point after reviewing other data that have come from similar source-memory paradigms.

Using a one-response test procedure, Li et al. (2004) had their young (18–24) and older (63–75) participants judge whether they had previously seen a picture and made a size judgment at encoding, whether they had previously viewed a picture and made a living/non-living judgment during study or whether the picture was new. Li et al. (2004) did not assess the mid-frontal EM effect. Rather, as this was a source-memory procedure in which presumably contextual detail had to be recovered in order to perform adequately, they concentrated on the ERP sign of recollection. In a condition in which performance was equated between young and older adults, the typical left-sided parietal EM effect was observed in young adults when comparing the ERPs to source-correct with those to CRs. By contrast, in older adults, there was no sign of the left-sided, recollection-based effect due to a large, overlapping left-sided negativity. However, in similar fashion to the Wegesin et al. (2002) data, over the right-hemiscalp, older, relative to young, adults showed equivalent magnitude parietal activity. Li et al. (2004) interpreted this to mean that, although the recollection-based effect was absent over left hemiscalp, the right-sided effect most likely reflected similar retrieval processes. As had also been suggested by Wegesin et al. (2002), Li et al. (2004) posited that the older-adult negativity reflected the reliance on and recovery of visual detail, based on data from investigations by Cycowicz et al. (2001), Friedman et al. (2005), and Johansson et al. (2002). In other words, they speculated that while young adults most likely used a conceptually based retrieval strategy, older adults recruited a fundamentally different, perceptually based strategy. Whether this could have reflected a "compensatory" brain response was not considered by these authors.

A more explicit interpretation of additional brain activity in older adults as compensatory was proposed by Swick et al. (2006). In their study, Swick et al. (2006) also recruited patients with frontal-lobe lesions with which to compare their older adults, as some authors have suggested that there is a qualitative similarity between these patients and older adults on certain aspects of EM performance (Stuss et al., 1996). Swick et al. (2006) used the two-response procedure described earlier. Unfortunately, these investigators did not measure their waveforms using the typical latency window (300–500 ms) when the effects of familiarity/conceptual priming are thought to occur (their window was 400–800 ms, more typical of the recollection effect). Nonetheless, relative to young adults (18–27), older adults (63–82) did not show evidence of the neural sign of recollection-based processing, not even over right-parietal scalp. Rather, in similar fashion to the data of Li et al. (2004) and Wegesin et al. (2002), a large, left-frontal negativity was present in the older-adult waveforms during the 400–800 ms interval, most likely reducing any left-sided, recollection-based effect that may have been present. The authors interpreted the presence of the negativity as reflecting "compensatory" brain activity which, if true, may have been ineffective, as the older adults performed reliably worse than their young-adult counterparts.

Interindividual variability in performance and ERP measures in older adults may indicate that EM decline is not an inevitable aspect of cognitive aging. Data that support this notion from an R/K-source-memory paradigm have been reported by Duarte et al. (2006). Young (18–25) and older (60–83) participants made R/K/New decisions and then, for any item judged R, indicated whether the picture had been studied under manipulability or animacy encoding instructions. Duarte et al. (2006) categorized their older-adult participants on the basis of their memory-sensitivity performance into old-high (equivalent performance to young adults) and old-low (lower performance than young adults) subgroups. Contrary to most studies of cognitive aging, older adults as a whole showed lower familiarity estimates than young adults (but, see discussion of Wang et al., 2012, below), whereas estimates of recollection were similar in old-high and young adults but, as one might expect, lower in old-low adults. The mid-frontal and recollection-based EM-effect data were fairly consistent with the behavioral data – young adults produced reliable signs of these processes, whereas both old-high and old-low subgroups did not show significant mid-frontal EM effects. By contrast, old-high participants showed a reliable recollection-based EM effect with a scalp distribution and magnitude similar to that of young adults. However, although old-low subjects displayed a robust old/new effect between 700 and 1200 ms, this difference was negative-going over left-frontal scalp, and was not present in the ERPs of the young or old-high adults. Duarte et al. (2006) considered whether their negative-going effect might have reflected compensatory brain activity to counter the reduction in both familiarity- and recollection-based processing, or "dedifferentiation," in which the old-low subgroup, unlike the young and old-high adults, could have recruited neural networks not specialized for the task at hand (see Reuter-Lorenz and Park, 2010, for further details). Duarte et al. (2006) could not come to a firm conclusion concerning which of these alternatives was more likely. Furthermore, as was true of the data of Wegesin et al. (2002), these investigators did not attempt to correlate the magnitude of this activity with mnemonic performance.

A similar decrement, relative to young adults (20–25) in the older-adult (61–81) recollection effect was observed by Friedman et al. (2010) in a source-memory paradigm in which initially meaningless, symbol-like objects were presented for study. By contrast, the mid-frontal EM effect appeared to be intact in these older adults. However, when Friedman et al. (2010) categorized their older adults into good and poor performers on the basis of memory sensitivity, only the old-high subgroup showed evidence of the mid-frontal and left-parietal EM effects; they were not present in the ERPs of the old-low subgroup. Rather, the ERPs of the low-performing older group were characterized, as in the Duarte et al. (2006) investigation, by a left-frontal negative EM effect (∼600–900 ms) that could have reflected compensation for the reduced familiarity- as well as recollection-based processing in this group.

As the data were preliminary and the two subgroups had small *N*s ($N = 8$), these data need to be considered with caution.

The majority of the investigations of source-memory reviewed above employed sources that were most likely not chosen on the basis of older adults' performance and, therefore, might not have been optimal for inducing good contextual-memory retrieval in these participants (all sources are not created equal; see Spencer and Raz, 1995). In an attempt to boost the source-memory performance of their older adults (59–75) relative to young adults (19–29), Dulas et al. (2011) used contexts manipulated by the type of judgment made during encoding while participants viewed pictures of common objects. They hypothesized that the self-referential nature of pleasantness judgments (is this item pleasant to you?) relative to self-external, "commonness" judgments would enhance the source-memory performance of older adults (Symons and Johnson, 1997). Although pleasantness relative to commonness judgments led to significantly greater source accuracy in both older and young adults, young adults still reliably outperformed their older-adult counterparts during the retrieval phase for words encoded under both conditions. Intriguingly, however, the neural sign of recollection was of equivalent magnitude in young and older adults, although the mid-frontal EM effect was smaller in older adults. Importantly, recollection-based neural activity was larger in the self-referential compared to the self-external condition, but only in older adults. Hence, it appears that, at least from the ERP data, older adults benefited more from the encoding manipulation than did young adults. Based on the interpretation that the recollection-related effect reflects the amount of contextual detail recovered from EM (Wilding, 2000; Vilberg et al., 2006), this finding suggests, by contrast with most age-related investigations, that the number of details recollected was greater in older adults for correct-source judgments associated with self-referential compared to self-external experiences.

In a similar attempt to employ episodes that were likely to be as well remembered in older ($M = 68.3$; $SD = 2.7$) as in young adults ($M = 22.7$; $SD = 2.5$), Eppinger et al. (2010) first asked participants to learn common-object-reward pairings (positive, +50 cents; negative, −50 cents; neutral, 0). Volunteers were given 15 trials of each object-reward pairing and then were administered an Old/New recognition series for the objects. For any item judged "old," they then had to state the "source," i.e., was the object associated with positive- or negative-feedback. Their experiment was based on the finding that older adults tend to remember stimuli that have positive valences, relative to those that are negative. Eppinger et al. (2010) suggested that this implied that older adults have a positive memory bias for self-relevant information. Unlike many previous investigations, older adults showed equivalent memory sensitivity during Old/New recognition as well as source-memory, most likely as a result of the large number of repetitions during study. The mid-frontal EM effect (250–400 ms) was of similar magnitude in young and older adults, but only for objects that had been paired with positive feedback. By contrast with previous studies, the putative recollection-based effect (450–700 ms) was characterized by a right-frontal topography in young as well as older adults for correct-source judgments to objects associated with both positive- and negative-feedback. However, consistent with several of the studies reviewed above, while the young adults also exhibited an EM effect at left-parietal sites for both types of feedback (between 450 and 700 ms), this left-sided activity was absent in the ERPs of the older adults. The right-frontal nature of the scalp distribution during the 450–700 ms interval renders unclear its association with recollection (but, see the interpretation by Li et al., 2004), although the concomitant left-sided positive activity does imply such a relation, at least in young adults. Perhaps, as Eppinger et al. (2010) posit, positive feedback has a greater effect on familiarity- than recollection-based recognition. On this view, older adults might have been able to base their judgments on familiarity rather than recollection, presumably accounting for their, respectively, intact and absent, mid-frontal and left-parietal EM effects. The authors concluded that the findings suggested that their older adults attributed a greater degree of emotional valence to positive feedback (the "positivity effect," see Mather and Carstensen, 2005) during memory acquisition, which may have counteracted older adults' well-documented decline in source memory.

To obtain a better handle on age-related changes in the putative familiarity-related EM effect, Wang et al. (2012) employed a modified R/K procedure with words based upon the hypothesis that familiarity relies on a graded memory-strength signal (Yonelinas, 2002). In the procedure used by Wang et al. (2012), R judgments are assumed to reflect recollection-based retrievals. Rather than using a single "Know" judgment (which could include retrieval of items with widely varying memory strengths), Wang et al. (2012) sorted "non-recollected" old items (i.e., those not given an R judgment) according to the confidence rating participants assigned to these items – confident old, unconfident old, unconfident new, and confident new. Based on these data, unlike the majority of behavioral data noted earlier, both familiarity- and recollection-based behavioral estimates were lower, relative to young adults (18–28) in older adults (63–76). While their young adults showed a gradation in mid-frontal EM effect magnitude (300–500 ms; R > confident old > confident new), these conditions did not differ in the ERPs of the older adults, nor did older participants produce a reliable mid-frontal effect (as was also the case in Duarte et al., 2006). By contrast, for both young and older adults, the recollection-based EM effect (500–800 ms) was significantly larger to items given an R judgment relative to confident old and confident new judgments (the latter two did not differ for either group). Of note, and consistent with several previous reports, the older, relative to the young, adults produced a reliably smaller recollection-based effect. The major conclusion reached by Wang et al. (2012) was that, relative to young adults, the putative familiarity-based retrievals of older adults may have depended on qualitatively different cognitive mechanisms that might not have been observable at the scalp.

In sum, the results of source-memory investigations suggest a more complex picture than that emerging from studies of recognition memory. Nonetheless, when it has been measured, the mid-frontal EM effect findings again indicate a great degree of between-study variability. This effect's magnitude can be equivalent in young and older adults, or smaller in older adults, as well as absent in older relative to young adults, the latter occurring even in high-performing subgroups of elderly individuals (e.g., Duarte et al., 2006). This variability mirrors that observed in many

investigations of cognitive aging, especially when age groups are categorized on a variable that declines with age (e.g., executive function; working-memory capacity). I will consider age-related variability in a separate section of the discussion below. Like the recognition-related data reviewed earlier, the source-memory findings do not appear to support, in any simple fashion, a role for conceptual priming in modulating the magnitude of the mid-frontal effect. For example, it would be difficult to reconcile the conceptual priming account with the Wang et al. (2012) finding of a relation between graded-confidence and mid-frontal effect magnitude. Finally, the data are also equivocal with respect to whether the retrieval-related brain activity of older adults benefits more from pictorial than verbal stimuli as memoranda.

The results for the putative recollection-based EM effect are somewhat more consistent. Several source-memory studies have revealed the presence of either a centrally- or left-frontally focused negativity (larger to old than new items) that tends to overlap and thereby reduce the magnitude of any left-parietal EM effect that might be present. This negative-going activity is thought by some investigators to be compensatory (but see Discussion below). However, in these situations, older adults tend to produce right-parietal activity that has been interpreted as reflecting the same retrieval operations as its left-parietal counterpart (Li et al., 2004).

STEM CUED-RECALL

Free-recall is arguably the ultimate and most valid technique for assessing recollection-based processing, as neither a copy cue nor a word-stem is available to guide retrieval. Hence, the participant must engage a conscious, effortful strategy for mind-traveling that will maximize the number of items recalled. Generally, older, relative to young, adults perform worse on free-recall than they do on recognition (Craik and McDowd, 1987). Word-stem cued-recall is a step removed, as the three-letter stem serves as a cue to aid retrieval of the complete word (that is, the word that was on the study list). Although previous authors have investigated the brain's electrical activity in young adults in this type of paradigm (e.g., Allan et al., 1996, 2000), to my knowledge, only Angel and colleagues have used the word-stem, cued-recall task in age-related studies (Angel et al., 2009, 2010, 2011). In the Allan and colleagues' studies with young adults, a positive-going, cued-recall EM effect was observed that exhibited an early left-sided, temporo-parietal scalp topography, and a subsequent right-frontal scalp distribution. Nonetheless, the cued-recall effect behaved similarly to the left-parietal recollection effect elicited in standard Old/New and source-memory recognition tasks. That is, it was larger to items studied under deep than shallow semantic-encoding conditions (Rugg et al., 1998; Allan et al., 2000), and to correct compared to incorrect source retrievals (Allan and Rugg, 1998). Allan et al. (2000) concluded that the cued-recall EM effect received contributions from the generators giving rise to the left-predominant, recollection effect as well as those responsible for producing the longer-duration, right-prefrontal EM effect. Because cued-recall necessitates the reinstatement of a word given only the word's stem, it arguably recruits greater executive control processes relative to recognition. This might account for the presence of the right-frontal EM effect.

An important methodological feature of the word-stem, cued-recall paradigm is the ability to distinguish between an "explicit" (i.e., episodic) and an "implicit" memory retrieval (i.e., due to repetition priming). The former is operationalized as completing a word-stem with an item that was on the study list and is judged to be "old." The latter is defined as completing a word-stem with an item that was on the study list but is unrecognized as having been on that list (Allan et al., 1996). Another important feature in these studies is the "baseline" completion condition, i.e., word stems completed with an appropriate word, but one that was not on the study list and is judged correctly to be "new." One shortcoming in all of the Angel et al. studies reviewed below is that these investigators did not compute putative "implicit" word-stem completion averages. Hence, they could not comment on the presence in the electrical record of components that might have reflected such, presumably, non-conscious, implicit retrievals. In the first investigation by Angel et al. (2009) using the stem-cued paradigm, these authors compared the ERPs elicited by correctly rejected, baseline stem completions with those stems completed by studied items correctly recognized as old. Angel et al. (2009) observed putative recollection-based EM effects in the young- ($M = 21$; SD = 1.9) as well as older-adult ($M = 65$; SD = 3.3) age group, which did not differ in magnitude. However, no scalp maps were available to determine the similarity of these effects to those already published. Nonetheless, Angel et al. (2009) claimed that, whereas the young adults' topography was left-sided, that of the older adults was bilaterally distributed. They noted that this asymmetry was similar to the HAROLD pattern (Hemispheric Asymmetry Reduction in the Old) observed in some of the hemodynamic data of older adults (Cabeza, 2002) and, on this basis, suggested that older adults had "compensated." Nevertheless, it remains unclear what the older adults had compensated for, or whether such "compensation" was effective, because these participants performed reliably more poorly than their young-adult counterparts. Further, no attempt was made to relate this activity to performance measures.

In an attempt to obtain more information on variability in the older-adult population, in a second investigation using the same paradigm, Angel et al. (2010) explored the relations between educational level (often used as a proxy for cognitive-reserve; Stern, 2002) and behavioral word-stem, cued-recall performance, and ERP EM effects. Angel et al. (2010) divided their young ($M = 25$; SD = 1.9) and older ($M = 66$; SD = 5) participants at the median into low- (LE) and high-education (HE) groups, each with Ns of 14. The major finding was that the older-adult HE group showed better memory accuracy than its LE counterpart. The effect of education was not significant for the young, most likely due to the greater homogeneity in this group. The major ERP finding was that, relative to the LE group, both young- and older-adult HE groups showed larger putative, recollection-based parietal EM effects. Nonetheless, the young HE recollection effect was reliably larger than that of the old HE group suggesting, as noted earlier that, relative to the young, even high-performing older-adult groups may recover fewer contextual details during retrieval. These data add to the currently limited ERP evidence that older-adult samples cannot be considered homogeneous, and that level of education may exert a positive effect on the memory performance

and associated brain activity of some older-adult individuals (see also, Czernochowski et al., 2008).

In a second exploration of age-related variability in neurocognitive indices, Angel et al. (2011) again employed the word-stem, cued-recall paradigm. As in their previous study (Angel et al., 2009), Angel et al. (2011) observed left-lateralized recollection-based EM effects in their young participants (23–26) but bilaterally symmetrical effects in their older adults (60–80), which they again interpreted as compensatory within the framework of the HAROLD model (Cabeza, 2002). Relative to older adults, the left-sided, young-adult recollection-based effect was significantly larger. However, as best as can be determined, the presumed recollection-based EM effect was only reliable for the young adults and was not significant for the older adults, in accord with other studies reviewed in this section.

In summary, although only explored by a single laboratory, the word-stem cued-recall data suggest that, relative to young adults, older adults retrieve a smaller amount of information when correctly completing a stem with a previously studied word. Hence, these data join those resulting from recognition-, source-, and R/K-memory experiments. On the other hand, it would be helpful to have other, independent, laboratories confirm these age-related, word-stem, cued-recall findings. Nonetheless, whether the right-lateralized activity observed in older participants in these cued-recall investigations is truly compensatory has not been vigorously tested (see section on Compensation below).

DISCUSSION

FAMILIARITY VS. RECOLLECTION

If the presumption that the left-parietal EM effect reflects the amount of contextual detail recovered from EM is valid, then the majority of studies reviewed above suggest, as do their behavioral counterparts, that recollection-based processing is deficient in older adults. In several studies, this magnitude reduction has been associated with lower performance in older-adult samples. Nonetheless, even when performance was matched (e.g., Li et al., 2004), or high-performing older adults were compared to young adults (Angel et al., 2010), these older individuals still exhibited smaller recollection-based EM effects (but see Duarte et al., 2006). Then again, the picture of the cognitive aging of familiarity-based processing is less clear. This state of affairs is due, in no small measure, to the current controversy concerning whether the mid-frontal EM effect reflects familiarity and/or conceptual priming. Hence, even if the magnitude findings were consistent (which they clearly are not) it would be difficult to come to a definitive conclusion. Blurring the picture even further is the fact that the behavioral findings point clearly to the preservation or minimal disruption of both episodic familiarity-based processing (e.g., Howard et al., 2006) and conceptually based implicit memory (i.e., priming; Monti et al., 1996; Fleischman and Gabrieli, 1998; Fleischman, 2007). This makes the absence of the mid-frontal EM effect in some studies difficult to understand (but, see Wang et al., 2012 for one interpretation). Adding to the problem of reaching an informed conclusion is the fact that, with few exceptions (e.g., Wang et al., 2012), many investigators have assumed that the mid-frontal EM effect reflects familiarity without collecting behavioral proxies that could validate the presence of this type of processing (e.g., R/K judgments). To disambiguate these two potential contributors to the processes reflected by the mid-frontal EM effect might also require a conceptual-priming manipulation, as has been argued for by Paller and his associates (e.g., Paller et al., 2012). This is especially true of the studies of the canonical Old/New recognition-memory paradigm, in which most investigators have used the mid-frontal EM effect as a proxy for familiarity, without collecting a relevant behavioral measure that would enable them to conclude, on a more definitive basis, that this indeed was the case. Nonetheless, as noted earlier, it is difficult to reconcile the finding of a strong relation between confidence ratings and mid-frontal EM effect magnitude (e.g., Wang et al., 2012) with a conceptual-fluency account of the data (see also, Rosburg et al., 2011 and Mecklinger et al., 2012).

One possibility for the absence of a putative, familiarity-based neural signature in some of the studies reviewed above is that other, earlier-occurring processes contribute to recognition-memory decisions. For example, Tsivilis et al. (2001) reported that the amplitude of an early EM effect (between 100 and 300 ms), with a fronto-polar scalp distribution was more consistent with a familiarity-based effect than the mid-frontal EM effect, which was also present in their waveforms (see also, Duarte et al., 2004). This early latency effect is consistent with primate data (Brown and Bashir, 2002) that suggests that a "familiarity-based" signal can occur quite early, at around 100 ms, well before the peak of the human mid-frontal activity. Hence, it is possible that, in some of the age-related investigations reviewed above, investigators, choosing to measure the purported 300–500 ms "familiarity" interval, may have missed early onset, hit vs. correct-rejection differences. This bears future investigation.

In addition to familiarity and recollection, other mechanisms are known to contribute to the retrieval of information during recognition memory. For example, a perceptual, implicit-memory mechanism might be responsible for the brain's relatively automatic retrieval of a previously experienced event in the absence of conscious awareness about that episode. Though not without its difficulties, repetition priming is one way of operationalizing this putatively implicit or indirect influence. Because the processing fluency of an item is increased via repetition, increments in fluency can lead participants to judge an item as having been previously studied (Jacoby and Dallas, 1981). As older adults are relatively unimpaired on repetition-priming tasks relative to direct or explicit (i.e., episodic) memory (Friedman et al., 1993), one might expect the neural correlates of such processes to be preserved in older relative to young adults (to the extent that they can be observed at the scalp). Although some work in this domain has been performed with young adults (Friedman, 2004; Woollams et al., 2008; Yu and Rugg, 2010; Lucas et al., 2012), such data are missing in studies of cognitive aging. This could be a productive area of future research.

Two major, but alternative hypotheses have been advanced to explain the functional significance of the left-parietal EM effect elicited during the retrieval phases of recognition-memory paradigms: (1) it could reflect internal attentional orienting to mental representations retrieved from EM (see Vilberg and Rugg, 2008 for review); or (2) it could reflect neural activity that aids the online representation of recollected information (Vilberg and

Rugg, 2009; Rugg and Vilberg, 2013), including the possibility that it might indicate the engagement of the episodic buffer postulated by Baddeley (2000) in his updated account of working memory (Vilberg and Rugg, 2008). Given the age-related data reviewed above, it would be difficult to argue for one interpretation over the other. However, the majority of the evidence, which is based solely on young-adult data, appears to support the second alternative. Nonetheless, the data on the viability of the episodic-buffer hypothesis is scarce. Hence, to the extent that the recollection-based EM effect indexes similar processes in young and older adults would imply that the older-adult recollection effect most likely indexes the amount of information (i.e., contextual details) retrieved from long-term memory. On this view, as noted previously, older adults do not appear to retrieve as many details as their young-adult counterparts.

COMPENSATION

The question of whether older adults recruit electrical activity that reflects "compensatory" processes to counteract deficits in mnemonic cognition was raised earlier. This idea, that older adults might bring "new" neural networks online (not recruited by the young) to thwart cognitive decline, was first observed in the PET/fMRI literature (e.g., Cabeza et al., 2002). This very attractive hypothesis implies plasticity in the aging brain, an idea that was, until the advent of neuroimaging, thought to be relatively untenable. However, while some authors argue that compensatory fMRI and ERP brain activity should only be evident in high-performing older adults (Cabeza et al., 2002; Riis et al., 2008), there are fMRI/PET and ERP data that show additional activity in *poorly performing* older adults (Fabiani et al., 1998; Nielson et al., 2002; Colcombe et al., 2005; Friedman et al., 2010). Hence, the issue of the functional significance of this type of additional brain activity is quite unsettled. Moreover, in many of these reports, precisely which cognitive processes are being compensated for is often not discussed. It is also unclear, in some investigations, whether the compensatory activity is correlated positively with performance, which arguably it ought to be, if such activity presumably benefits older-adult cognition.

These same criticisms apply to the limited ERP compensation-related data mentioned earlier. Nonetheless, ERP data may be better able to identify the kinds of processes reflected by such additional brain activity than slower techniques such as fMRI. For instance, if the compensatory activity is recruited to counter the reduction in recollection-based processing and enhance the recovery of information encoded in the previous episode's memory trace, then that activity should most likely occur prior to the recognition-memory decision (Johnson et al., 2013). Indeed, in the Nessler et al. (2007) study described in the recognition-memory section, the retrieval-related, putatively compensatory, left-frontal negative-going activity preceded participants' EM judgments by several hundred milliseconds. In fact, following up the Nessler et al. (2007) investigation, Johnson et al. (2013) elicited highly similar, retrieval-related, compensatory activity in young adults by disrupting episodic encoding (i.e., semantic elaboration) during the study phase. Like the Nessler et al. (2007) data, this retrieval-related activity had a scalp focus over the left inferior prefrontal cortex (LIPFC), a brain region implicated heavily in the control and retrieval of semantic information (e.g., Badre and Wagner, 2007). Similarly, the activity preceded the memory judgment by several hundred milliseconds and, importantly, its magnitude was correlated positively with memory accuracy. Hence, "compensation" is not limited to older adults. Rather, such activity can occur at any point in the lifespan, as suggested recently by Reuter-Lorenz and Park (2010) in their "scaffolding" account of compensation-related brain activity.

An inkling of the processes this activity might have reflected in the Johnson et al. (2013) investigation comes from an event-related fMRI study by Raposo et al. (2009), in which episodic retrieval was made difficult by limiting the amount of semantic information at encoding that could be integrated into EM traces. Similar to Johnson et al. (2013), though with better spatial resolution, these investigators observed compensatory activity over LIPFC at retrieval (i.e., this activity was correlated positively with performance) for items that were difficult to recover by virtue of the reduced semantic elaboration they had received during encoding. Raposo et al. (2009) interpreted this area of activation as indexing the recovery of episodic information that proceeded by highlighting the semantic memories that were generated during encoding. Because of the similarity in the topographic maps (Johnson et al., 2013) and areas of hemodynamic activation (Raposo et al., 2009) in the two investigations, Johnson et al. (2013) invoked a similar explanation to account for the compensatory activity that they observed over LIPFC.

Part of the difficulty in specifying which particular processes are invoked is due to the large disparities in cognitive ability between young and older adults and the use of young-elderly group comparisons to define and/or assess compensatory activity. Hence, our use of within-group comparisons of young adults with presumably intact cognitive abilities appears to have aided in elucidating the timing and nature of the underlying processes that might account for the presence of compensatory activity in young and older adults (see Johnson et al., 2013, for a complete discussion).

AGE-RELATED VARIABILITY

Finally, I come to a brief discussion of the greater variability typically associated with the performance and ERP data of older-adult samples (Morse, 1993). Several investigations of age-related change have noted increases in interindividual variability in older age groups (e.g., Frias et al., 2007). As we have seen, one investigative team (Duarte et al., 2006) used recognition-memory test performance to divide their older adults into low- and high-performing subgroups, and found large differences in recollection-based processing (favoring the high-performing subgroup) between the two older-adult subgroups. Similarly, Angel et al. (2010), following the cognitive-reserve hypothesis (see Stern, 2002 and discussion below), categorized their groups into those with low- and high-educational status and showed reliable effects of high-educational status in older adults on both performance measures and recollection-based brain activity (see Czernochowski et al., 2008 for a similar effect of socio-economic status in a recency/recognition paradigm). These data suggest that the cognitive-reserve hypothesis might provide a reasonable account for the increased variability observed in old age, although other

hypotheses reviewed briefly at the end of this section might also explain these data.

Our group has also taken a foray into this area of research in an attempt to determine if recollection-based processing would differ in older-adult samples categorized according to their executive-function performance. Because there are data indicating that some memory paradigms (for example, free-recall) require good executive skills to perform adequately (e.g., Taconnat et al., 2007) and, as noted earlier, older adults perform worse on free-recall compared to recognition (Craik and McDowd, 1987), our older-adult participants were categorized into those who were low- and high- on the basis of a series of executive-function assessments [the manipulation and maintenance of information in WM – assessed by reading and computation spans; task-set switching, a quintessential executive task; and the Eriksen flanker test (Eriksen and Eriksen, 1974), which yields a measure of inhibition]. **Figure 4** depicts preliminary ERP data elicited during a study/test recognition-memory paradigm in which items were presented either one or three times during encoding and tested in initial (30-min following study) and final (1-h following study) recognition-memory assessments (Radin et al., unpublished observations). Note that the categorization of the older-adult data into low- and high-performers neatly orders the magnitude of the recollection-based parietal EM effect: Young > Old-High > Old-Low. This ordering also held for the memory sensitivity or accuracy of the three groups. Clearly, those older adults who scored well on the tests of executive function are those who produce the largest recollection-based electrical activity. Nonetheless, as has been noted throughout this review, the high-performing older adults do not reach the level of putative recollection-based processing shown by their young-adult counterparts. This again suggests that older, relative to young, adults do not recover the same amount of information when interrogating their EM traces. Although speculative, the larger recollection effect in the old-high, relative to the old-low, participants might be due to more efficient retrieval strategies, presumably instantiated in the prefrontal cortex and its interconnections where the computations involved in executive processes are thought to take place. On the other hand, the old-high group may have encoded the items more deeply, creating relatively richly detailed memory traces (again, with greater strategic control than their old-low counterparts), thereby rendering their recollection-based retrievals more facile. The similar or differential contributions of encoding and retrieval to age-related memory performance and brain activity are clearly questions for further, individual-difference ERP research.

A few theories have been advanced to account for the greater variability in older compared to younger adults. One of the most popular, the tenets of which were described earlier, is the compensation account (Cabeza et al., 2002), which has recently been modified and updated by Park and Reuter-Lorenz (2009) in their "scaffolding" model of compensatory brain activity. This latter theoretical stance posits that the recruitment of additional brain activity and, presumably, cognitive processes, is an adaptive response that can occur at any point along the lifespan (see Park and Reuter-Lorenz, 2009 and Reuter-Lorenz and Park, 2010, for reviews). A second, influential explanation is the cognitive-reserve hypothesis (Stern, 2002), which posits that certain factors (i.e., IQ, occupational, and educational status) provide buffers that mitigate the effects of age-related brain insult on cognitive function. This hypothesis suggests that older adults with high levels of reserve capacity (defined by these proxy measures) may be better able to maintain normal cognitive function throughout old age than their low-reserve counterparts (see, for an example, the Angel et al., 2010 investigation reviewed earlier). However, the division of the data into low and high groups based on some salient variable is silent about how long these differences have existed. For example, they may have been present since birth (possibly genetic) or since early childhood and young adulthood and maintained throughout middle and old age. The third hypothesis, one that is complimentary to that of cognitive-reserve, takes this possibility into account. The "brain maintenance" model of memory aging (Nyberg et al., 2012) postulates that those older individuals who have, since their young-adults days, maintained their neurocognitive abilities at high levels, are those who age "successfully." On the other hand, at the current stage of knowledge it is entirely unclear which of these models can best account for the ERP/cognitive-aging data that have so far been collected.

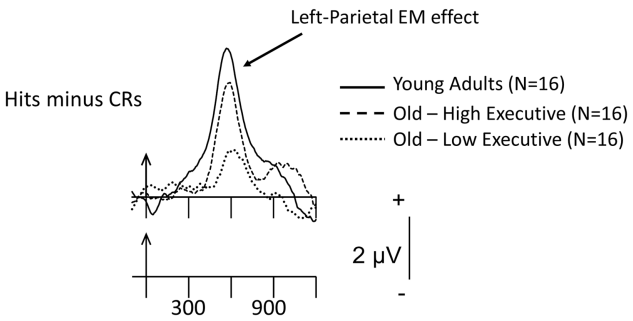


FIGURE 4 | Grand-mean Hits minus CR difference ERPs for items presented three times during study, averaged across the 16 young adults, 16 old-high executive function (EF), and 16 old-low EF subgroups at the left-parietal scalp site, P3. Arrows mark stimulus onset, with time markers every 300 ms. The waveforms for the three groups have been superimposed. These preliminary data were recorded during the final recognition-memory test phase, which took place 1 h following the initial test series.

CONCLUSION AND FUTURE DIRECTIONS

This survey of the ERP/memory and aging literature indicates that the neural evidence for disruption or preservation of familiarity (and/or conceptual priming) is extremely mixed and I can draw no firm conclusion at this time. On the other hand, the data suggest that, in many circumstances, recollection-based processing is diminished in older adults, in accord with much of the behavioral literature. However, there are clearly individual differences among older adults in the extent to which this facility is disrupted. The study of interindividual variability has a long history in cognitive-aging research (Botwinick and Thompson, 1968). However, from the perspective of the ERP technique, the unraveling of the underlying sources of age-related variability is clearly in its infancy. As a whole, the scant individual-difference data reviewed above, including putative "compensatory" brain activity,

indicate, as highlighted by others (Duarte et al., 2006), that older adults cannot be considered a homogeneous population and that deficits in EM are not an inexorable consequence of aging. Hence, mnemonic function may be amenable to improvement through cognitive-training regimens (Lustig et al., 2009; Greenwood and Parasuraman, 2010). For example, one documented deficit is that some older adults do not engage in self-initiated processing to encode items into and retrieve items from EM because environmental support may be lacking (Craik, 2008). Hence, this might be one processing strategy that could be trained in older adults with documented memory deficits.

Additional investigations of "compensation" are needed to validate the construct (at least in the ERP domain), understand the nature of the antecedent conditions that lead older (and younger) adults to recruit novel neural networks and to understand the cognition that this extra brain activity reflects. Similarly, preliminary evidence from this laboratory (Czernochowski et al., 2008; Radin et al., unpublished observations; **Figure 4**) and others (Angel et al., 2010) indicates that some life-style variables, such as socio-economic status and level of educational attainment, as well as level of executive function may modulate the extent to which mnemonic processes are disrupted in older adults. Further investigation of the influence of these and similar variables should be undertaken. Similarly, the cognitive-reserve, compensation and brain-maintenance hypotheses, and the older-adult variability they were created to explain, make clear that it is now time to assess their efficacy in explaining the ERP/cognitive-aging data that have been and will be recorded in the future. To conclude, understanding the basis of individual differences and how to exploit them to enable older adults to maintain their EM function at a high level are important goals for future investigations of the neurocognitive aging of memory.

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REFERENCES

Allan, K., Doyle, M. C., and Rugg, M. D. (1996). An event-related potential study of word-stem cued recall. *Brain Res. Cogn. Brain Res.* 4, 251–262. doi:10.1016/S0926-6410(96)00061-4

Allan, K., Robb, W. G., and Rugg, M. D. (2000). The effect of encoding manipulations on neural correlates of episodic retrieval. *Neuropsychologia* 38, 1188–1205. doi:10.1016/S0028-3932(00)00013-0

Allan, K., and Rugg, M. D. (1998). Neural correlates of cued recall with and without retrieval of source memory. *Neuroreport* 9, 3463–3466. doi:10.1097/00001756-199810260-00023

Ally, B. A., Simons, J. S., McKeever, J. D., Peers, P. V., and Budson, A. E. (2008a). Parietal contributions to recollection: electrophysiological evidence from aging and patients with parietal lesions. *Neuropsychologia* 46, 1800–1812. doi:10.1016/j.neuropsychologia.2008.02.026

Ally, B. A., Waring, J. D., Beth, E. H., McKeever, J. D., Milberg, W. P., and Budson, A. E. (2008b). Aging memory for pictures: using high-density event-related potentials to understand the effect of aging on the picture superiority effect. *Neuropsychologia* 46, 679–689. doi:10.1016/j.neuropsychologia.2007.09.011

Angel, L., Fay, S., Bouazzaoui, B., Baudouin, A., and Isingrini, M. (2010). Protective role of educational level on episodic memory aging: an event-related potential study. *Brain Cogn.* 74, 312–323. doi:10.1016/j.bandc.2010.08.012

Angel, L., Fay, S., Bouazzaoui, B., Granjon, L., and Isingrini, M. (2009). Neural correlates of cued recall in young and older adults: an event-related potential study. *Neuroreport* 20, 75–79. doi:10.1097/WNR.0b013e32831b6e0c

Angel, L., Fay, S., Bouazzaoui, B., and Isingrini, M. (2011). Two hemispheres for better memory in old age: role of executive functioning. *J. Cogn. Neurosci.* 23, 3767–3777. doi:10.1162/jocn_a_00104

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends Cogn. Sci. (Regul. Ed.)* 4, 417–423. doi:10.1016/S1364-6613(00)01538-2

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–2901. doi:10.1016/j.neuropsychologia.2007.06.015

Botwinick, J., and Thompson, L. W. (1968). A research note on individual differences in reaction time in relation to age. *J. Genet. Psychol.* 112, 73–75.

Braver, T. S., and Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neurosci. Biobehav. Rev.* 26, 809–817. doi:10.1016/S0149-7634(02)00067-2

Brown, M. W., and Bashir, Z. I. (2002). Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1083–1095. doi:10.1098/rstb.2002.1097

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* 44, 195–208. doi:10.1016/j.neuron.2004.09.006

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol. Aging* 17, 85–100. doi:10.1037/0882-7974.17.1.85

Cabeza, R., Anderson, N. D., Locantore, J. K., and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17, 1394–1402. doi:10.1006/nimg.2002.1280

Colcombe, S. J., Kramer, A. F., Erickson, K. I., and Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol. Aging* 20, 363–375. doi:10.1037/0882-7974.20.3.363

Craik, F. I. (2008). Memory changes in normal and pathological aging. *Can. J. Psychiatry* 53, 343–345.

Craik, F. I. M., and McDowd, J. M. (1987). Age differences in recall and recognition. *J. Exp. Psychol. Learn. Mem. Cogn.* 13, 474–479. doi:10.1037/0278-7393.13.3.474

Curran, T. (2000). Brain potentials of recollection and familiarity. *Mem. Cognit.* 28, 923–938. doi:10.3758/BF03209340

Cycowicz, Y. M., Friedman, D., and Snodgrass, J. G. (2001). Remembering the color of objects: an ERP investigation of source memory. *Cereb. Cortex* 11, 322–334. doi:10.1093/cercor/11.4.322

Czernochowski, D., Fabiani, M., and Friedman, D. (2008). Use it or lose it? SES mitigates age-related decline in a recency/recognition task. *Neurobiol. Aging* 29, 945–958. doi:10.1016/j.neurobiolaging.2006.12.017

Duarte, A., Ranganath, C., Trujillo, C., and Knight, R. T. (2006). Intact recollection memory in high-performing older adults: ERP and behavioral evidence. *J. Cogn. Neurosci.* 18, 33–47. doi:10.1162/089892906775249988

Duarte, A., Ranganath, C., Winward, L., Hayward, D., and Knight, R. T. (2004). Dissociable neural correlates for familiarity and recollection during the encoding and retrieval of pictures: an ERP study. *Brain Res. Cogn. Brain Res.* 18, 255–272. doi:10.1016/j.cogbrainres.2003.10.010

Dulas, M. R., Newsome, R. N., and Duarte, A. (2011). The effects of aging on ERP correlates of source memory retrieval for self-referential information. *Brain Res.* 1377, 84–100. doi:10.1016/j.brainres.2010.12.087

Duverne, S., Motamedinia, S., and Rugg, M. D. (2009). Effects of age on the neural correlates of retrieval cue processing are modulated by task demands. *J. Cogn. Neurosci.* 21, 1–17. doi:10.1162/jocn.2009.21001

Eppinger, B., Herbert, M., and Kray, J. (2010). We remember the good things: age differences in learning and memory. *Neurobiol. Learn. Mem.* 93, 515–521. doi:10.1016/j.nlm.2010.01.009

Eriksen, B. A., and Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept. Psychophys.* 16, 143–149. doi:10.3758/BF03203267

Fabiani, M., Friedman, D., and Cheng, J. C. (1998). Individual differences in P3 scalp distribution in older adults, and their relationship to frontal lobe function. *Psychophysiology* 35, 698–708. doi:10.1111/1469-8986.3560698

Fleischman, D. A. (2007). Repetition priming in aging and Alzheimer's disease: an integrative review and future directions. *Cortex* 43, 889–897. doi:10.1016/S0010-9452(08)70688-9

Fleischman, D. A., and Gabrieli, J. D. E. (1998). Repetition priming in normal aging and Alzheimer's disease: a review of findings and theories. *Psychol. Aging* 13, 88–119. doi:10.1037/0882-7974.13.1.88

Frias, C. M., de Lövdén, M., Lindenberger, U., and Nilsson, L.-G. (2007). Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. *Intelligence* 35, 381–392. doi:10.1016/j.intell.2006.07.011

Friedman, D. (1990). ERPs during continuous recognition memory for words. *Biol. Psychol.* 30, 61–87. doi:10.1016/0301-0511(90)90091-A

Friedman, D. (2000). Event-related brain potential investigations of memory and aging. *Biol. Psychol.* 54, 175–206. doi:10.1016/S0301-0511(00)00056-9

Friedman, D. (2004). ERP studies of recognition memory: differential effects of familiarity, recollection and episodic priming. *Cogn. Sci.* 1, 81–121.

Friedman, D. (2007). "A neurocognitive overview of aging phenomena based on the event-related potential (ERP)," in *Cognitive Reserve*, ed. Y. Stern (Amsterdam: Swets), 285–303.

Friedman, D., Cycowicz, Y. M., and Bersick, M. (2005). The late negative episodic memory effect: the effect of recapitulating study details at test. *Brain Res. Cogn. Brain Res.* 23, 185–198. doi:10.1016/j.cogbrainres.2004.10.005

Friedman, D., de Chastelaine, M., Nessler, D., and Malcolm, B. (2010). Changes in familiarity and recollection across the lifespan: an ERP perspective. *Brain Res.* 1310, 124–141. doi:10.1016/j.brainres.2009.11.016

Friedman, D., Hamberger, M., and Ritter, W. (1993). Event-related potentials as indicators of repetition priming in young and older adults: amplitude, duration, and scalp distribution. *Psychol. Aging* 8, 120–125. doi:10.1037/0882-7974.8.1.120

Friedman, D., and Johnson, R. (2000). Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microsc. Res. Tech.* 51, 6–28. doi:10.1002/1097-0029(20001001)51:1<6::AID-JEMT2>3.0.CO;2-R

Friedman, D., Nessler, D., and Johnson, R. Jr. (2007). Memory encoding and retrieval in the aging brain. *Clin. EEG Neurosci.* 38, 2–7. doi:10.1177/155005940703800105

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi:10.1038/nrn3256

Greenwood, P. M., and Parasuraman, R. (2010). Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. *Front. Aging Neurosci.* 2:150. doi:10.3389/fnagi.2010.00150

Guillaume, C., Clochon, P., Denise, P., Rauchs, G., Guillery-Girard, B., Eustache, F., et al. (2009). Early age-related changes in episodic memory retrieval as revealed by event-related potentials. *Neuroreport* 20, 191–196. doi:10.1097/WNR.0b013e32831b44ca

Gutchess, A. H., Ieuji, Y., and Federmeier, K. D. (2007). Event-related potentials reveal age differences in the encoding and recognition of scenes. *J. Cogn. Neurosci.* 19, 1089–1103. doi:10.1162/jocn.2007.19.7.1089

Hayama, H. R., Johnson, J. D., and Rugg, M. D. (2008). The relationship between the right frontal old/new ERP effect and post-retrieval monitoring: specific or non-specific? *Neuropsychologia* 46, 1211–1223. doi:10.1016/j

Howard, M. W., Bessette-Symons, B., Zhang, Y., and Hoyer, W. J. (2006). Aging selectively impairs recollection in recognition memory for pictures: evidence from modeling and receiver operating characteristic curves. *Psychol. Aging* 21, 96–106. doi:10.1037/0882-7974.21.1.96

Jacoby, L. L., and Dallas, M. (1981). On the relationship between autobiographical memory and perceptual learning. *J. Exp. Psychol. Gen.* 110, 306–340. doi:10.1037/0096-3445.110.3.306

Jacques, P. L. St., and Levine, B. (2007). Ageing and autobiographical memory for emotional and neutral events. *Memory* 15, 129–144. doi:10.1080/09658210601119762

Jennings, J. M., and Jacoby, L. L. (1993). Automatic versus intentional uses of memory: aging, attention, and control. *Psychol. Aging* 8, 283–293. doi:10.1037/0882-7974.8.2.283

Johansson, M., Stenberg, G., Lindgren, M., and Rosen, I. (2002). Memory for perceived and imagined pictures – an event-related potential study. *Neuropsychologia* 40, 986–1002. doi:10.1016/S0028-3932(01)00148-8

Johnson, R. Jr., Kreiter, K., Russo, B., and Zhu, J. (1998). A spatio-temporal analysis of recognition-related event-related brain potentials. *Int. J. Psychophysiol.* 29, 83–104. doi:10.1016/S0167-8760(98)00006-3

Johnson, R. (1995). "Event-related potential insights into the neurobiology of memory systems," in *Handbook of Neuropsychology*, Vol. 10, eds F. Boller and J. Grafman (Amsterdam: Elsevier), 135–163.

Johnson, R., Nessler, D., and Friedman, D. (2013). Temporally specific divided attention tasks in young adults reveal the temporal dynamics of episodic encoding failures in elderly adults. *Psychol. Aging* 28, 443–456. doi:10.1037/a0030967

Koen, J., and Yonelinas, A. (2013). Recollection and familiarity declines in healthy aging, aMCI, and AD. *J. Cogn. Neurosci.* 25(Suppl.), 197.

Kutas, M., and Hillyard, S. A. (1980). Reading between the lines: event-related brain potentials during natural sentence processing. *Brain Lang.* 11, 354–373. doi:10.1016/0093-934X(80)90133-9

Li, J., Morcom, A. M., and Rugg, M. D. (2004). The effects of age on the neural correlates of successful episodic retrieval: an ERP study. *Cogn. Affect. Behav. Neurosci.* 4, 279–293. doi:10.3758/CABN.4.3.279

Light, L. L. (1991). Memory and aging: four hypotheses in search of data. *Annu. Rev. Psychol.* 42, 333–376. doi:10.1146/annurev.ps.42.020191.002001

Lucas, H. D., Taylor, J. R., Henson, R. N., and Paller, K. A. (2012). Many roads lead to recognition: electrophysiological correlates of familiarity derived from short-term masked repetition priming. *Neuropsychologia* 50, 3041–3052. doi:10.1016/j.neuropsychologia.2012.07.036

Lustig, C., Shah, P., Seidler, R., and Reuter-Lorenz, P. A. (2009). Aging, training, and the brain: a review and future directions. *Neuropsychol. Rev.* 19, 504–522. doi:10.1007/s11065-009-9119-9

Mandler, G. (1980). Recognizing: the judgement of previous occurrence. *Psychol. Rev.* 87, 252–271. doi:10.1037/0033-295X.87.3.252

Mather, M., and Carstensen, L. L. (2005). Aging and motivated cognition: the positivity effect in attention and memory. *Trends Cogn. Sci. (Regul. Ed.)* 9, 496–502. doi:10.1016/j.tics.2005.08.005

McDaniel, M. A., Jacoby, L. L., and Einstein, G. O. (2008). "New considerations in aging and memory: the glass may be half full," in *The Handbook of Cognition and Aging*, Vol. 3, eds F. I. M. Craik and T. A. Salthouse (New York: Psychology Press), 251–310.

McElree, B., Dolan, P. O., and Jacoby, L. L. (1999). Isolating the contributions of familiarity and source information to item recognition: a time course analysis. *J. Exp. Psychol. Learn. Mem. Cogn.* 25, 563–582. doi:10.1037/0278-7393.25.3.563

Mecklinger, A. (2000). Interfacing mind and brain: a neurocognitive model of recognition memory. *Psychophysiology* 37, 565–582. doi:10.1111/1469-8986.3750565

Mecklinger, A. (2010). The control of long-term memory: brain systems and cognitive processes. *Neurosci. Biobehav. Rev.* 34, 1055–1065. doi:10.1016/j.neubiorev.2009.11.020

Mecklinger, A., Frings, C., and Rosburg, T. (2012). Response to Paller etal.: the role of familiarity in making inferences about unknown quantities. *Trends Cogn. Sci. (Regul. Ed.)* 16, 315–316. doi:10.1016/j.tics.2012.04.009

Monti, L. A., Gabrieli, J. D. E., Reminger, S. L., Rinaldi, J. A., Wilson, R. S., and Fleischman, D. A. (1996). Differential effects of aging and Alzheimer's disease on conceptual implicit and explicit memory. *Neuropsychology* 10, 101–112. doi:10.1037/0894-4105.10.1.101

Morcom, A. M., and Rugg, M. D. (2004). Effects of age on retrieval cue processing as revealed by ERPs. *Neuropsychologia* 42, 1525–1542. doi:10.1016/j.neuropsychologia.2004.03.009

Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychol. Aging* 8, 156–164. doi:10.1037/0882-7974.8.2.156

Nessler, D., Friedman, D., Johnson, R. Jr., and Bersick, M. (2007). Does repetition engender the same retrieval processes in young and older adults? *Neuroreport* 18, 1837–1840. doi:10.1097/WNR.0b013e3282f16d9f00001756-200711190-00017

Nessler, D., Johnson, R., Bersick, M., and Friedman, D. (2006). On why the elderly have normal semantic retrieval but deficient episodic encoding: a study of left inferior frontal ERP activity. *Neuroimage* 30, 299–312. doi:10.1016/j.neuroimage.2005.09.005

Nessler, D., Mecklinger, A., and Penney, T. B. (2001). Event related brain potentials and illusory memories: the effects of differential encoding. *Brain Res. Cogn. Brain Res.* 10, 283–301. doi:10.1016/S0926-6410(00)00049-5

Nielson, K. A., Langenecker, S. A., and Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychol. Aging* 17, 56–71. doi:10.1037/0882-7974.17.1.56

Nyberg, L., Lovden, M., Riklund, K., Lindenberger, U., and Backman, L. (2012). Memory aging and brain maintenance. *Trends Cogn. Sci. (Regul. Ed.)* 16, 292–305. doi:10.1016/j.tics.2012.04.005

Olichney, J. M., Van Petten, C., Paller, K. A., Salmon, D. P., Iragui, V. J., and Kutas, M. (2000). Word repetition in amnesia: electrophysiological measures of impaired and spared memory. *Brain* 123(Pt 9), 1948–1963. doi:10.1093/brain/123.9.1948

Paller, K. A. (2004). Electrical signals of memory and of the awareness of remembering. *Curr. Dir. Psychol. Sci.* 13, 49–55. doi:10.1111/j.0963-7214.2004.00273.x

Paller, K. A., Lucas, H. D., and Voss, J. L. (2012). Assuming too much from 'familiar' brain potentials. *Trends Cogn. Sci. (Regul. Ed.)* 16, 313–315. doi:10.1016/j.tics.2012.04.010

Park, D. C., and Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu. Rev. Psychol.* 60, 173–196. doi:10.1146/annurev.psych.59.103006.093656

Perrin, F., Pernier, J., Bertrand, O., and Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalogr. Clin. Neurophysiol.* 72, 184–187. doi:10.1016/0013-4694(89)90180-6

Prull, M. W., Dawes, L. L., Martin, A. M. III, Rosenberg, H. F., and Light, L. L. (2006). Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. *Psychol. Aging* 21, 107–118. doi:10.1037/0882-7974.21.1.107

Ranganath, C., and Paller, K. A. (1999). Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron* 22, 605–613. doi:10.1016/S0896-6273(00)80714-X

Raposo, A., Han, S., and Dobbins, I. G. (2009). Ventrolateral prefrontal cortex and self-initiated semantic elaboration during memory retrieval. *Neuropsychologia* 47, 2261–2271. doi:10.1016/j.neuropsychologia.2008.10.024

Reuter-Lorenz, P. A., and Park, D. C. (2010). Human neuroscience and the aging mind: a new look at old problems. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 65, 405–415. doi:10.1093/geronb/gbq035

Riis, J. L., Chong, H., Ryan, K. K., Wolk, D. A., Rentz, D. M., Holcomb, P. J., et al. (2008). Compensatory neural activity distinguishes different patterns of normal cognitive aging. *Neuroimage* 39, 441–454. doi:10.1016/j.neuroimage.2007.08.034

Rosburg, T., Mecklinger, A., and Frings, C. (2011). When the brain decides: a familiarity-based approach to the recognition heuristic as evidenced by event-related brain potentials. *Psychol. Sci.* 22, 1527–1534. doi:10.1177/0956797611417454

Rugg, M. D., and Curran, T. (2007). Event-related potentials and recognition memory. *Trends Cogn. Sci. (Regul. Ed.)* 11, 251–257. doi:10.1016/j.tics.2007.04.004

Rugg, M. D., Mark, R. E., Walla, P., Schloerscheidt, A. M., Birch, C. S., and Allan, K. (1998). Dissociation of the neural correlates of implicit and explicit memory. *Nature* 392, 595–598. doi:10.1038/33396

Rugg, M. D., and Morcom, A. M. (2005). "The relationship between brain activity, cognitive performance and aging: the case of memory," in *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*, eds R. Cabeza, L. Nyberg, and D. Park (New York: Oxford University Press), 132–154.

Rugg, M. D., and Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr. Opin. Neurobiol.* 23, 255–260. doi:10.1016/j.conb.2012.11.005

Rugg, M. D., and Yonelinas, A. P. (2003). Human recognition memory: a cognitive neuroscience perspective. *Trends Cogn. Sci. (Regul. Ed.)* 7, 313–319. doi:10.1016/S1364-6613(03)00131-1

Senkfor, A. J., and Van Petten, C. (1998). Who said what: an event-related potential investigation of source and item memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 24, 1005–1025. doi:10.1037/0278-7393.24.4.1005

Smith, M. E. (1993). Neurophysiological manifestations of recollective experience during recognition memory judgements. *J. Cogn. Neurosci.* 5, 1–13. doi:10.1162/jocn.1993.5.1.1

Spencer, W. D., and Raz, N. (1995). Differential effects of aging on memory for content and context: a meta-analysis. *Psychol. Aging* 10, 527–539. doi:10.1037/0882-7974.10.4.527

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460. doi:10.1017/S1355617702813248

Stuss, D. T., Craik, F. I. M., Sayer, L., Franchi, D., and Alexander, M. P. (1996). Comparison of older people and patients with frontal lesions: evidence from word list learning. *Psychol. Aging* 11, 387–395. doi:10.1037/0882-7974.11.3.387

Swick, D., Senkfor, A. J., and Van Petten, C. (2006). Source memory retrieval is affected by aging and prefrontal lesions: behavioral and ERP evidence. *Brain Res.* 1107, 161–176. doi:10.1016/j.brainres.2006.06.013

Symons, C. S., and Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol. Bull.* 121, 371–394. doi:10.1037/0033-2909.121.3.371

Taconnat, L., Clarys, D., Vanneste, S., Bouazzaoui, B., and Isingrini, M. (2007). Aging and strategic retrieval in a cued-recall test: the role of executive functions and fluid intelligence. *Brain Cogn.* 64, 1–6. doi:10.1016/j.bandc.2006.09.011

Trott, C. T., Friedman, D., Ritter, W., Fabiani, M., and Snodgrass, J. G. (1999). Episodic priming and memory for temporal source: event-related potentials reveal age-related differences in prefrontal functioning. *Psychol. Aging* 14, 390–413. doi:10.1037/0882-7974.14.3.390

Tsivilis, D., Otten, L. J., and Rugg, M. D. (2001). Context effects on the neural correlates of recognition memory. An electrophysiological study. *Neuron* 31, 497–505. doi:10.1016/S0896-6273(01)00376-2

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi:10.1037/h0080017

Verhaeghen, P. (2011). Aging and executive control: reports of a demise greatly exaggerated. *Curr. Dir. Psychol. Sci.* 20, 174–180. doi:10.1177/0963721411408772

Vilberg, K. L., Moosavi, R. F., and Rugg, M. D. (2006). The relationship between electrophysiological correlates of recollection and amount of information retrieved. *Brain Res.* 1122, 161–170. doi:10.1016/j.brainres.2006.09.023

Vilberg, K. L., and Rugg, M. D. (2008). Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. *Neuropsychologia* 46, 1787–1799. doi:10.1016/j.neuropsychologia.2008.01.004

Vilberg, K. L., and Rugg, M. D. (2009). Functional significance of retrieval-related activity in lateral parietal cortex: evidence from fMRI and ERPs. *Hum. Brain Mapp.* 30, 1490–1501. doi:10.1002/hbm.20618

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Quinn, B. T., et al. (2006). The functional and structural significance of the frontal shift in the old/new ERP effect. *Brain Res.* 1081, 156–170. doi:10.1016/j.brainres.2006.01.076

Wang, T. H., de Chastelaine, M., Minton, B., and Rugg, M. D. (2012). Effects of age on the neural correlates of familiarity as indexed by ERPs. *J. Cogn. Neurosci.* 24, 1055–1068. doi:10.1162/jocn_a_00129

Wegesin, D. J., Friedman, D., Varughese, N., and Stern, Y. (2002). Age-related changes in source memory retrieval: an ERP replication and extension. *Brain Res. Cogn. Brain Res.* 13, 323–338. doi:10.1016/S0926-6410(01)00126-4

Wilding, E. L. (2000). In what way does the parietal ERP old/new effect index recollection? *Int. J. Psychophysiol.* 35, 81–87. doi:10.1016/S0167-8760(99)00095-1

Wilding, E. L., and Rugg, M. D. (1996). An event-related potential study of recognition memory with and without retrieval of source. *Brain* 119(Pt 3), 889–905. doi:10.1093/brain/119.4.1415-a

Wolk, D. A., Sen, N. M., Chong, H., Riis, J. L., McGinnis, S. M., Holcomb, P. J., et al. (2009). ERP correlates of item recognition memory: effects of age and performance. *Brain Res.* 1250, 218–231. doi:10.1016/j.brainres.2008.11.014

Woodruff, C. C., Hayama, H. R., and Rugg, M. D. (2006). Electrophysiological dissociation of the neural correlates of recollection and familiarity. *Brain Res.* 1100,

125–135. doi:10.1016/j.brainres.2006.05.019

Woollams, A. M., Taylor, J. R., Karayanidis, F., and Henson, R. N. (2008). Event-related potentials associated with masked priming of test cues reveal multiple potential contributions to recognition memory. *J. Cogn. Neurosci.* 20, 1114–1129. doi: 10.1162/jocn.2008.20076

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517. doi:10.1006/jmla.2002.2864

Yu, S. S., and Rugg, M. D. (2010). Dissociation of the electrophysiological correlates of familiarity strength and item repetition. *Brain Res.* 1320, 74–84. doi:10.1016/j.brainres.2009.12.071

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ORIGINAL RESEARCH
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Role of Aging and Hippocampus in Time-Place Learning: Link to Episodic-Like Memory?

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Introduction: With time-place learning (TPL), animals link an event with the spatial location and the time of day (TOD). The what–where–when TPL components make the task putatively episodic-like in nature. Animals use an internal sense of time to master TPL, which is circadian system based. Finding indications for a role of the hippocampus and (early) aging-sensitivity in TPL would strengthen the episodic-like memory nature of the paradigm.

Methods: Previously, we used C57Bl/6 mice for our TPL research. Here, we used CD1 mice which are less hippocampal-driven and age faster compared to C57Bl/6 mice. To demonstrate the low degree of hippocampal-driven performance in CD1 mice, a cross maze was used. The spontaneous alternation test was used to score spatial working memory in CD1 mice at four different age categories (young (3–6 months), middle-aged (7–11 months), aged (12–18 months) and old (>19 months). TPL performance of middle-aged and aged CD1 mice was tested in a setup with either two or three time points per day (2-arm or 3-arm TPL task). Immunostainings were applied on brains of young and middle-aged C57Bl/6 mice that had successfully mastered the 3-arm TPL task.

Results: In contrast to C57Bl/6 mice, middle-aged and aged CD1 mice were less hippocampus-driven and failed to master the 3-arm TPL task. They could, however, master the 2-arm TPL task primarily via an ordinal (non-circadian) timing system. c-Fos, CRY2, vasopressin (AVP), and phosphorylated cAMP response element-binding protein (pCREB) were investigated. We found no differences at the level of the suprachiasmatic nucleus (SCN; circadian master clock), whereas CRY2 expression was increased in the hippocampal dentate gyrus (DG). The most pronounced difference between TPL trained and control mice was found in c-Fos expression in the paraventricular thalamic nucleus, a circadian system relay station.

Conclusions: These results further indicate a key role of CRY proteins in TPL and confirm the limited role of the SCN in TPL. Based on the poor TPL performance of CD1 mice, the results suggest age-sensitivity and hippocampal involvement in TPL. We suspect that TPL reflects an episodic-like memory task, but due to its functional nature, also entail the translation of experienced episodes into semantic rules acquired by training.

Keywords: learning, circadian, memory, aging, time, place, cry, clock genes

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INTRODUCTION

Natural environments show many daily dynamics. The availability of food, mates and predators varies across both space and time. If these stimuli vary predictably, it is advantageous for animals to learn this spatiotemporal day-to-day variability. The ability to encode spatiotemporal reoccurring events, and to exploit this information by efficiently organized daily activities, is believed to constitute a significant fitness advantage which has likely shaped the architecture of cognitive and circadian systems over the course of evolution. Indeed, the ability to learn spatiotemporal variability has been demonstrated in many species and has become known as time-place learning (TPL; for a review, see Mulder et al., 2013a). In TPL, animals have to link a stimulus with the location and the time of day (TOD). In our TPL paradigm (Van der Zee et al., 2008; Mulder et al., 2013a), food deprived mice are confronted with a conflict between a positive reinforcer (food reward) and a negative reinforcer (mild footshock) in a three-arm maze depending on the TOD. The paradigm emulates the natural situation in which hungry animals seek food while different feeding locations (arms of the maze) can be predictably safe or unsafe to visit in a TOD-dependent manner (Van der Zee et al., 2008). Investigating TPL can help to gain better understanding of the foraging dynamics in prey or predators. Besides this ecological relevance, TPL is interesting in the field of Neuroscience. Animals can use their circadian system for TPL, referred to as circadian TPL (cTPL). cTPL depends on *Cry*, but not *Per* clock genes (Van der Zee et al., 2008; Mulder et al., 2013b). However, insights into the specific role of the circadian system in memory formation is limited (Van der Zee et al., 2009; Mulder et al., 2013a; Smarr et al., 2014; and references therein). Moreover, cTPL does not depend on the circadian master clock, the suprachiasmatic nucleus (SCN) or rhythmic release of corticosteron from the adrenals (Mulder et al., 2014). Therefore, cTPL must be primarily driven by non-SCN oscillators such as hippocampal cell assemblies, although the SCN may still play a modulatory role.

The components what–where–when in TPL make the task putatively episodic-like in nature. The "what" component is the food reward vs. the mild footshock at the food location, the "where" is one of the three arms, and the "when" is the TOD, predicting which arm can be visited for a food reward without getting the mild but aversive footshock. cTPL implies that distinct phases of an internal circadian clock can be incorporated in associative "what–where–when" memory. This type of memory is particularly susceptible to perturbations of aging and neurodegenerative diseases affecting the hippocampus, yet animal models to study episodic memory or episodic-like memory are scarce (Binder et al., 2015 and references therein).

Two typical aspects of episodic memory are the hippocampus-dependent and aging-sensitive nature of the task. To further explore to what extent cTPL is aging-sensitive, our first aim is to examine the CD1 mouse in a variety of behavioral studies including TPL. CD1 mice differ in the degree of hippocampal contribution to learning and memory performance as compared to C57Bl6 mice. The CD1 (albino) mouse is one of the most commonly used outbred stock, also in spatial learning tasks (see Patil et al., 2012, and references therein). The mice of this strain age relatively fast compared to C57Bl/6 mice (Chia et al., 2005; Johnson, 2014). Studies in mice (Havekes et al., 2011), rats (Begega et al., 2001), and humans (Yamamoto and Degirolamo, 2012) show that aged individuals tend to switch from a hippocampal-driven strategy to a striatal—driven strategy to solve spatial tasks, mainly because of the gradual loss of hippocampal function and aging-related loss of hippocampal neurogenesis and spine-plasticity needed for memory formation (Kuhn et al., 1996; Gil-Mohapel et al., 2013; Van der Zee, 2015). Adult hippocampal neurogenesis is required for spatial learning, since inhibition of hippocampal neurogenesis can impair spatial relational memory (whereas boosting adult neurogenesis by way of running wheel activity strongly improves hippocampus-dependent learning; van Praag et al., 2005; Van der Borght et al., 2007). Higher proliferation and higher neuronal survival has been shown in the hippocampus of C57Bl/6 mice compared to CD1 mice. On the other hand, higher net neurogenesis, higher volume of the DG and more granule cells have been found in CD1 mice (Kempermann et al., 1997; Gage, 2002), possibly to compensate for reduced hippocampal functioning. Moreover, equal environmental enrichment is more effective in stimulating hippocampal neurogenesis in C57Bl/6 mice than CD1 mice (Gage, 2002), suggesting a less flexible hippocampal system in the latter strain. It is not known how these differences in hippocampal neurogenesis and the higher rate of aging relate to TPL performance in CD1 mice. Therefore, the (aged) CD1 mouse seems a suitable strain to test whether mastering the TPL task is sensitive to relative poor hippocampal functioning.

As cTPL presumes a functional connection between the circadian system and memory system(s), our second aim is to explore putative neurobiological correlates of cTPL. This was done using immunohistochemistry (IHC) in brain sections from young and middle-aged C57Bl/6 mice that had successfully mastered the cTPL task. The markers we chose were c-Fos, CRY2, AVP, and pCREB. C-Fos belongs to the immediate early gene (IEG) family of transcription factors. Because IEGs are rapidly induced by neuronal activity, c-Fos is widely used as a marker for activated circuits at cellular scale (Morgan et al., 1987; Sagar et al., 1988; Kawashima et al., 2014). CRY2 is the transcription product of the core molecular clock gene Cry2 (Cryptochrome 2). The Cry genes are specifically interesting to investigate as neuronal markers for TPL, as TPL depends on Cry1 and/or Cry2 (Van der Zee et al., 2008), but not Per1 and Per2 clock genes (Mulder et al., 2013b). AVP (arginine vasopressin) is seen as the major output signal of the SCN master clock (Kalsbeek et al., 2010). Approximately 10–30% of the neurons within the SCN contain AVP. Vasopressin is indicated as the (humoral) output of the SCN because AVP producing SCN neurons project to distal targets areas, such as to the paraventricular nucleus (PVT). But AVP also has excitatory action within the SCN acting on the V1-type receptors (Kalamatianos et al., 2004). Salient events have been shown to induce a circadian rhythm in the expression of muscarinic acetylcholine receptors in the SCN, with peak expression levels

coinciding with the event-specific TOD (Van der Zee et al., 2004). It has therefore been proposed that the SCN may function as a programmable "alarm clock", using the neuropeptide AVP as an output to transfer the specific TOD information to other brain regions (Biemans et al., 2003; Van der Zee et al., 2004; van der Veen et al., 2008; Hut and Van der Zee, 2011). pCREB is a widely used marker for neuronal plasticity. CREB (cAMP response element-binding protein) is a cellular transcription factor which binds to certain DNA sequences called cAMP response elements (CRE), thereby increasing or decreasing the transcription of downstream genes. The phosphorylated form of CREB (pCREB) has been shown to be integral in the formation of spatial memory. Moreover, pCREB has a well-documented role in neuronal plasticity and protein synthesis-dependent long-term memory formation in diverse behavioral paradigms among many species (Bernabeu et al., 1997; Guzowski and McGaugh, 1997; Lamprecht et al., 1997; Colombo et al., 2003; Countryman et al., 2005). pCREB stimulates the expression of several IEGs. One of those genes is the proto-oncogene transcription factor c-Fos (Sheng and Greenberg, 1990). These four markers could provide a first glance of the neuronal substrate underlying cTPL.

Taken together, the current experimental data may shed more light on: (a) the age-sensitivity of cTPL in a strain-dependent manner and (b) the neuronal substrate underlying TPL. These findings may help to determine to what extent TPL can be viewed as an episodic-like memory task.

MATERIALS AND METHODS

Animals and Housing

Male mice were housed individually in macrolon type II cages (length 35 cm, width 15 cm, height 13.5 cm, Bayer, Germany), with sawdust as bedding and shredded cardboard as nesting material. The mice were kept in a climate room with controlled temperature (22 ± 1°C) and humidity (55 ± 10%). A light/dark (LD) schedule (12 h light-12 h dark; lights on at 07:00 h GMT+1 h) was maintained. Light intensity was always 20–50 lux measured between the cages. Food (standard rodent chow: RMHB/2180, Arie Block BV, Woerden, Netherlands) was available *ad libitum*, except during food deprivation (cross maze and TPL testing). Normal tap water was available *ad libitum*. Cages were cleaned at least once every 2 weeks. All mice were checked daily for food/water/health/activity/abnormal behavior. The protocol was approved by the ethical committee for the use of experimental animals of the University of Groningen. All efforts were made to minimize the number of animals used and their discomfort. For this study four age categories are defined as follows: young (3–6 months), middle-aged (7–11 months), aged (12–18 months), and old (>19 months). An overview of the used mice and the age categories is provided in **Table 1**.

Cross Maze Test

To test for strain-dependent preferences for a hippocampal-driven strategy in place learning, a cross maze consisting of a small chamber with transparent ceiling and four arms (tubes) arising from it was used. For each mouse, the following protocol was used: 5 days before the beginning of the experiment mice were food deprived. Testing started when the body weight of the mice was about 85% of their body weight at the start of the experiment. The experiment was divided into three phases: the habituation phase lasted 1 day on which each mouse performed two trials with a 3 min interval (during which mice remained in their home cage in the experimental room). The mouse was put in a transporter cage which was then connected to the maze. It entered the maze from the south arm, while the north arm was closed. During the first trial, four small pieces of food were present (standard rodent chow; one piece of food was approximately the size of a pencil tip), two in the beginning of the right and left arm and two at the end of those arms. During the second trial, only the end of the right and left arms were baited with food (one piece of food per arm). When the mouse entered the maze, the way back to the transporter cage was blocked. The mouse was allowed to exit the maze from the same arm it got in after it had consumed all the food, or when 5 min had passed. After each trial the maze was cleaned with 30% ethanol and towel-dried. The next phase was the training phase. Each mouse performed six trials per day with a 3 min interval after each trial. Mice entered again from the south arm, while the north arm was closed. It this phase, only one arm was baited with food (randomized between mice). Under the perforated non-baited arm, a small piece of food was present (not visible and out of reach of the mouse) to rule out the possibility that mice selected the correct arm by olfactory cues. Mice had to learn to visit the baited arm first in order to get to the food. The non-baited arm was then blocked and the mouse was allowed to exit the maze. A trial was considered successful if the mouse entered the baited arm first. The training phase ended when a mouse performed five correct trials in a row on a single day. The last phase was the testing phase in which the mouse performed only one trial. This time they entered the maze from the north arm, while the south arm was blocked. Both right and left arms were baited with food. If the mouse visited the trained arm first, it indicated a preference for a hippocampal-driven strategy.

Running Wheel Activity and Circadian Score

To measure internal clock stability, animals were housed in cages equipped with a running wheel (diameter 13.5 cm) for constant activity recording. An 11 day constant dim light (LL) period was introduced, during which the animals display their endogenous activity rhythm (free-run). For each mouse, daily activity onsets during this period were determined by using a high- and low pass filter (crossing of 24 h-, and 4 h running-means). A linear trend line was calculated through these onset data points and absolute distances from each onset data point to this trend line were determined. A "circadian score" for a mouse was calculated (defined by: [average of absolute distances from trend line]$^{-1}$ × 100%, creating a score ranging from 0–100%, higher values indicating more consistency in activity onsets under free-run conditions).

TABLE 1 | Overview of the mice used in the experiments.

Experiment	CD1		C57Bl/6		Remarks
	N	Age	*N*	Age	
cross maze	9	3–6 mo (Y)	15	3–6 mo (Y)	
	9	>19 mo (O)	8	>19 mo (O)	
SA and circadian score	8	3–6 mo (Y)			
	7*	7–11 mo (MA)			
	7*	12–18 mo (A)			
	4	>19 mo (O)			
3-arm TPL and 2-arm TPL	9	7–11 mo (MA)			3-arm TPL design
	7*	7–11 mo (MA)			2-arm TPL-design
	7*	12–18 mo (A)			2-arm TPL-design
3-arm TPL and Immunostaining (IHC)			7 + 8 HCC	3–6 mo (Y)	CRY2, AVP, c-Fos, pCREB
			9 + 5 HCC	7–11 mo (MA)	

Overview of the mice used in the cross maze, the spontaneous alternation test (SA), the circadian score experiment, and the 3-arm and 2-arm TPL test. For the immunostaining experiment, the age indicates the age at which the mice were sacrificed. CD1 mouse numbers indicated with an asterisk (*) are the same mice per age category used in the different tests. HCC: Home Cage Controls. IHC: Immunohistochemistry. Age categories are indicated between parentheses [Y: Young (3–6 months); MA: Middle-Aged (7–11 months); A: Aged (12–18 months); O: Old (>19 months)].

Spontaneous Alternation Test

This test (described before in more detail, see Mulder et al., 2013a) consisted of 8 min exploration trials in a three arm symmetrical maze and was based on the natural behavior of animals to explore locations that are novel or visited the longest time ago, relying on spatial working memory. An alternation was defined as a triplet of sequential unique location visits. The alternation score (SA score) was calculated by dividing the number of alternations by the total possible alternations, the latter being equal to the total number of entries minus two.

TPL Testing Procedure

The used TPL test apparatus and testing procedures were described before (**Figure 5A**, 3-arm TPL design; Van der Zee et al., 2008; Mulder et al., 2013a,b, 2014, 2015). Briefly, to induce food seeking behavior and voluntary location-choices, mice were food deprived to 85% of their *ad libitum* body weight, as individually determined by the average of three daily measurements prior to initiating food deprivation. To monitor bodyweight during testing, mice were weighed before each daily TPL test session and received an individual amount of food at the end of the light-phase (ZT10.5).

After habituation steps (as described previously in Van der Zee et al., 2008; Mulder et al., 2013a), TPL testing (2-arm TPL design or 3-arm TPL design; see **Figure 3**) was commenced. In each of the daily test sessions (lasting maximally 10 min per mouse; two daily sessions in the 2-arm TPL design and three daily sessions in the 3-arm TPL design; see **Figure 3**), mice were presented with two or three different feeding locations. The mice had to learn to avoid one "non-target" location, which changed depending on the TOD (i.e., session). As a punishment for visiting the non-target location, mice received a mild but aversive footshock (set to 620 volts; 0.09 mA; <1 s). All locations were baited with powdered standard rodent chow (<0.1g) so that mice could not identify the non-target/target location(s) based on sight/smell and had to use knowledge of circadian phase to discriminate the hazardous non-target location. A session was considered correct, on an individual level, only when the two target locations were visited first, avoiding the non-target location or visiting it lastly. Daily performance was calculated for each animal as the percentage of correct sessions and these performances were averaged, forming a learning curve over multiple testing days (**Figure 5B**). Mice were tested in their inactive (light-) phase. A session (session 1 in the 2-arm TPL design and session 1 or 2 in the 3-arm TPL design) can be skipped to determine whether the mouse mastered the task using a circadian or a ordinal (non-circadian) strategy (**Figure 4**). Performance should drop below chance level if mice use an ordinal (non-circadian) strategy, which is presumably less hippocampus dependent. Home cage control (HCC) mice were not TPL tested, but similarly food deprived. In the 2-arm TPL test, middle-aged and aged mice were alternated in order of testing, so that a potential "time of day effect" was equally divided over the two groups. The location of the shock-arm was also alternated between trials to exclude the possibility that mice follow potential scent trails of the previously tested animal. The maze was cleaned between trials with a wet paper cloth.

Collection and Processing of Brain Material

Mice (in couples of a HCC and TPL mouse) were sacrificed at the time of their first or second daily TPL test-session (deviation maximally 10 min). We selected these time points for practical reasons, but avoided selecting the third TPL session time point because expression of most clock genes is lower at the beginning of the light-phase. Hence, by choosing the earlier time points

we increased the detectability of potentially upregulated markers (compared to HCC mice) in anticipation of TPL testing.

Under deep pentobarbital anesthesia, mice were perfused transcardially for 1 min with 0.9% NaCl + 0.5% heparin (400U) in H_2O (15 ml/min), followed by 150 ml 4% paraformaldehyde (PF) in 0.1 M phosphate buffer (PB) for fixation. Brains were collected and further processed in Greiner cups (Greiner Bio-One, Container, PS, 15 ml, 40 × 24.5 mm snapdeks, cat #203170). Brains were postfixated for 24 h in 4% PF in 0.1 M PB, rinsed for 1 day in 0.01M phosphate buffered saline (PBS, pH 7.4) and then kept overnight in 30% sucrose in PBS cryoprotectant at 4°C. Brains were frozen the next day using liquid nitrogen and stored at −80°C until further processing. Brains were cut in coronal sections of 25 μm thick using a cryotome and stored at 4°C. Target areas were the SCN (these sections also containing the anterior PVT) which was cut from −0.34 to −0.70 relative to bregma, and the hippocampus (these sections also containing PVT and cortex) which was cut from −1.82 to −2.06 relative to bregma according to the mouse brain stereotaxic atlas (Franklin and Paxinos, 1997, Academic press, CA, USA). Sections were sequentially distributed over eight Greiner cups containing 0.01M PBS, to create multiple equal series that could be used for different immuno-stainings.

Immunohistochemistry

Three to five brain sections per mouse were used for each staining. Because similar protocols were used for each staining, only the procedures for the pCREB staining will be described as an example. Brain sections were rinsed three times for 5 min in TBS (0.01 M Tris-HCL + 0.9% NaCl, pH = 7.4), and were then placed in 0.3% H_2O_2 in TBS for 30 min. After rinsing the sections in TBS four times, 5 min each time, the primary antibody solution was added (Rabbit α-pCREB Millipore 1:1000 with 5% Normal Goat Serum and 0.1% Triton-X 100 in TBS). Sections were incubated overnight at room temperature on a shaker. After being rinsed with TBS eight times, for 10 min each time, the sections were incubated at room temperature for 2 h with the secondary antibody (biotinylated Goat anti-rabbit IgG Jackson 1:500 with 1% Normal Goat Serum and 0.1% Triton-X 100 in TBS). Next, sections were rinsed eight times with TBS for 10 min each time. After that, the sections were put in ABC complex (1:500 in TBS) for 2 h and then rinsed again eight times with TBS for 10 min each time. Finally, the labeled cells were visualized with diaminobenzidine (DAB, 0.7 mg/mL in H_2O; Sigma-Aldrich, Steinheim, Germany) with 0.1% H_2O_2 as a reaction initiator. The reaction was stopped by rinsing three times with TBS for 5 min each time, and stored overnight in TBS at 4°C. The following day, the slices were mounted from a 1% gelatin in aquadest solution onto microscopic glasses using a paintbrush. The sections were placed with the posterior side faced up (during cutting the left hemisphere was marked so it could be distinguished during mounting) and ordered from anterior to posterior. Sections were left to dry overnight. Next, sections were put through an alchohol-xylol concentration series and covered with a cover glass using DPX mountant. A similar protocol was used for the other immunostainings, using different primary, and matching secondary antibodies. For CRY2, the primary antibody used was rabbit polyclonal anti-mCRY2 (1:200, from Alpha Diagnostic, USA). The available antibody for CRY1, the paralog of CRY2, failed to give a specific signal. For c-Fos, a rabbit polyclonal anti-c-Fos AB-5 was used (1:8000, vector), and for AVP a monoclonal anti-AVP (1:1000, PS41, kindly supplied by Dr. H. Gainer, NIH, MD, USA; Bult et al., 1992; Gerkema et al., 1994) was used.

Quantification

For each staining, the most appropriate quantification method was determined. When only few specifically labeled cells were present in the area of interest or when a variable background was present, cells were manually counted through a microscope. This applies for CRY2 in the SCN and DG, and for c-Fos in the DG and PVT. For the other immunostainings, optical densities (OD) were measured at 50× magnification using a computerized image analysis system (Quantimet 550, Leica, Cambridge, UK). The OD is expressed in arbitrary units corresponding to gray levels. To correct for variability in background staining among sections, background labeling was measured in the corpus callosum and extracted from the OD of the area of interest. Bilateral measurements were averaged. The experimenter was blind to the treatment of individual animals during all cell counting and OD measurements. Because of the different quantification methods used, all results are expressed as percentage relative to the HCC group. Differences between TPL and HCC groups were tested by two-tailed unpaired *t*-tests using Microsoft Excel.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 5.01 (GraphPad software, Inc.). Non-parametric tests were used in case datasets did not pass the normality test for Gaussian distribution (Kolmogorov-Smirnov). Differences in cross maze performance were tested using the Fisher Exact test. Differences between groups were analyzed using *t*-tests or the Kruskal-Wallis test with Dunn's Multiple Comparison post-test. Differences from chance level were analyzed using one-sample *t*-test or the Wilcoxon Signed Rank Test. $P < 0.05$ was considered significant.

RESULTS

Cross Maze, Spontaneous Alternation Task and Circadian Rhythmicity

For an overview of the used mice (strain, number and age) and tasks see also **Table 1**. The cross maze task revealed that notably the old CD1 mice (N = 9; >19 months of age) are less hippocampal-driven than old C57Bl/6 mice (N = 8; >19 months of age) in a spatial learning task (**Figure 1**; Fisher exact test; p = 0.009). Out of the nine aged CD1 mice, none had a preference for a hippocampal-driven strategy. This clear bias towards a striatal-driven strategy indicates a reduced hippocampal functioning in the aged CD1 mice as compared to the aged C57Bl/6 mice. For young mice (N = 9 for both

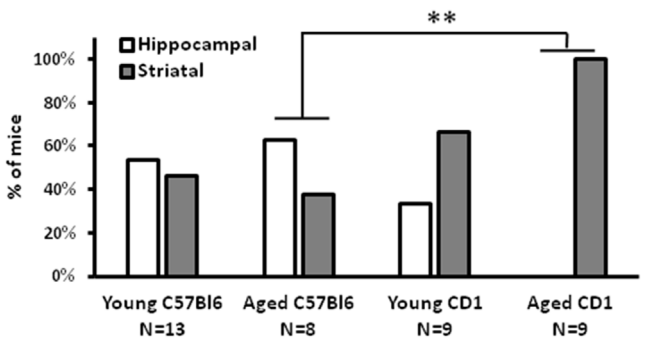


FIGURE 1 | Cross maze performance of CD1 mice. A strong preference for a striatal-driven strategy was found in aged CD1 mice, whereas in C57Bl/6 and young CD1 mice no clear preference for either a hippocampal- or striatal-driven strategy was present. $^{**}p < 0.01$, Fisher exact test.

strains; 3–6 months of age), such a difference was not present, although a higher percentage of young CD1 mice (67%) had a preference for a striatal-driven strategy as compared to the young C57Bl/6 mice (46%). These results demonstrate CD1 mice to be less hippocampal-driven than C57Bl/6 mice at young and particularly old age.

Next, we determined the impact of aging in the Spontaneous Alternation (SA) paradigm and the circadian organization of behavior based on running wheel activity (**Figure 2**). Spatial orientation and stability of the circadian system were measured, together with TPL performance, in middle-aged (N = 7; 7–11 months of age) and aged (N = 7; 12–18 months of age) male CD1 mice. **Figure 2** shows a representative actogram of a middle-aged and aged mouse, together with the calculated onset data points and trend line drawn through these. The upper left graph shows average circadian scores per age group. Two other groups of young (N = 8; 3–6 months of age) and old (N = 4; >19 months of age) male CD1 mice were included in this analysis. The circadian score declined with aging (Spearman $r = -0.69$, $p < 0.0001$). The Kruskal-Wallis test showed that the age groups were significantly different (KW statistic = 18.81; $p = 0.0003$). Dunn's post-test showed significant differences between young and aged ($p < 0.05$), young and old ($p < 0.001$), and middle-aged and old ($p < 0.05$) mice. Besides the circadian score extracted from the actograms, other signs of aging were also apparent, including increased fragmentation/noise and decreased general running wheel activity.

Performance in the SA paradigm was used as a measure of spatial working memory. Again, two additional age groups were tested to investigate more thoroughly the relation between aging on spatial working memory (young: N = 4; 3–6 months of age, old: N = 4; >19 months of age). The SA score stayed relatively robust with aging (Spearman $r = -0.04$, $p = 0.88$). The Kruskal-Wallis test showed that the age groups did not differ significantly from each other (KW statistic = 3.80; $p = 0.28$). Dunn's post-test showed no significant differences between age groups. Taken together, these results show that a decline of the strength in circadian organization of running wheel activity with aging in CD1 mice, indicating reduced functioning of the circadian system. In contrast, no such decline was found for SA performance. Of note, SA performance in C57Bl/6 mice in our hands is usually around 70% (Mulder et al., 2014), indicating that CD1 mice have a weaker SA performance than C57Bl/6 mice and hence a reduced hippocampal functioning as the hippocampus is a critical brain region for spatial working memory.

Time Place Learning in CD1 Mice: 3-arm- and 2-arm Design

The designs of the 2-arm and 3-arm TPL tasks are depicted in **Figure 3**. A schematic representation of the maze including the shock device is given in **Figure 5A**. In case of the 2-TPL setup, the middle arm was blocked. The study with nine middle-aged CD1 mice revealed that these mice were unable to learn the 3-arm TPL setup, irrespective of age. None of the mice were able to perform above the 33% chance level. For this reason a simpler TPL design was used in which fourteen CD1 mice (seven middle-aged and seven aged, (**Table 1**)—these are the same mice as used for the SA and circadian scores described above) had to associate only two locations at two different time points (sessions), with a chance level of 50% correct scores. Average group performance on the first 4 days did not differ significantly from chance level for both middle-aged and aged mice (mean 55.6% ± SD 16.0, Wilcoxon Signed Rank Test $p = 0.50$ and mean 48.6% ± SD 18.3, Wilcoxon Signed Rank Test $p = 0.78$ respectively, data not shown). Average group performances over the remaining last ten testing days (5–14) are shown in **Figure 4** (left panel). One sample t-test (two-tailed) showed that both middle-aged and aged mice performed significantly above chance level ($p = 0.049$ and $p = 0.01$, respectively). Results of middle-aged mice just reach significance, but mainly because of one low performing animal with an average performance of 40%. Unpaired t-test showed no significant difference between middle-aged and aged mice ($p = 0.71$, two-tailed).

Session skips reveal if animals use the skipped session as a cue in TPL and thus use an ordinal (non-circadian) strategy. When this is the case, performance should drop below chance level. The results of two separate morning session skips are shown on the right panel of **Figure 4**. Since the first session was skipped, performances represent daily group averages of only the second session. For comparison, a baseline for session 2 performance was determined based on 2 days before the first session skip and the 1 day between the first and second session skip.

For aged mice, performance after session skips was significantly different from baseline performance (Kruskal-Wallis test, $p = 0.026$). Dunn's post-test showed that performance after both individual session skips was significantly different from baseline performance ($p < 0.05$). Moreover, after both session skips, performance of aged mice was significantly below chance level (Wilcoxon Signed Rank Test, one-tailed, $p = 0.04$ in both cases). Together this indicates that the aged mice use an ordinal (non-circadian) strategy for TPL.

Session skipping also decreased average performance of middle aged mice compared to baseline, but less and not significantly (Kruskal-Wallis test, $p = 0.47$). Dunn's post-test

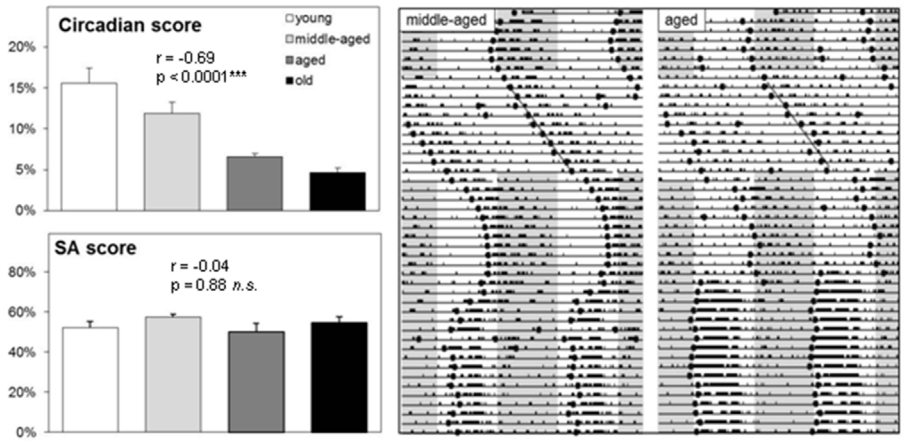


FIGURE 2 | Running wheel activity and spontaneous alternation (SA) performance of CD1 mice. Left: Group averages of circadian score and SA score (see text for further details on the correlations). Error bars represent SEM. Right: Representative double-plotted actograms (46 days) of a middle-aged and aged CD1 mouse. Gray areas indicate darkness (12:12 LD). Mice were kept under a 12:12 light-dark cycle, except during a constant light (LL) period of 11 days to asses free-run patterns. The circadian score was based on the average distance of calculated daily activity onsets (black dots) during LL to a linear trend line.

showed that performance after both session skips was not significantly different from baseline performance ($p > 0.05$ in both cases). After both session skips, performance did not fall significantly below chance level (Wilcoxon Signed Rank Test, one-tailed, $p = 0.15$ and $p = 0.39$ for the first and second session skip respectively). Overall, middle-aged mice seemed less affected by both session skips, suggesting that these mice may also partly rely on another strategy besides ordinal. Middle-aged mice showed an increase in performance (but not significant) after the second session skip compared to the first session skip which may indicate an adaptation due to the first session skip during which these animals may have learned that the ordinal (non-circadian) strategy is no longer reliable. Aged mice did not show this kind of adaptation.

Neuronal Substrate Candidates for (c)TPL

Two separate batches of C57Bl/6 mice were trained in the 3-arm TPL setup (**Table 1**). Young mice from the first batch were trained for 36 days, and middle-aged mice from the second batch were trained for 44 days. Learning curves from both batches were similar. The average learning curve is depicted in **Figure 5B**, which was comparable to previously published learning curves for the 3-arm TPL task (Van der Zee et al., 2008; Mulder et al., 2014). These mice were sacrificed the day after their last TPL

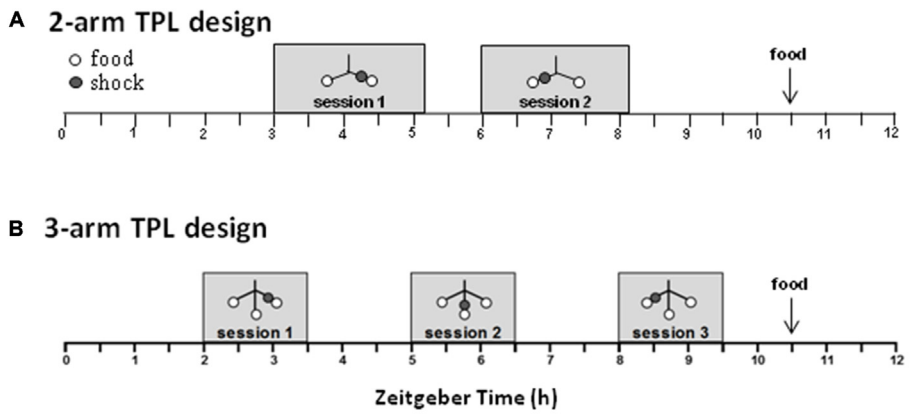


FIGURE 3 | Schematic overview of the daily time-place learning (TPL) testing protocol for two time points and two daily sessions (2-arm TPL design) or three time points and three daily sessions (3-arm TPL design). Mice had to learn to avoid one non-target location, which changed depending on the time of day (TOD; i.e., session). Open circles indicate food (powdered standard rodent chow, <0.1 g) at the end of an arm of the maze (see **Figure 5A**); gray circles indicate the (non-target) shock location. Mice were tested individually two or three times a day (depending on the design) in 10 min trials, with an intersession time of 3 h. Bodyweights were taken before each trial. Mice received an individual amount of food at the end of each day in order to maintain body weight at 85–87% of *ad libitum* feeding weight. Testing was performed in the light phase. ZT0 (zeitgeber time zero) indicates lights on.

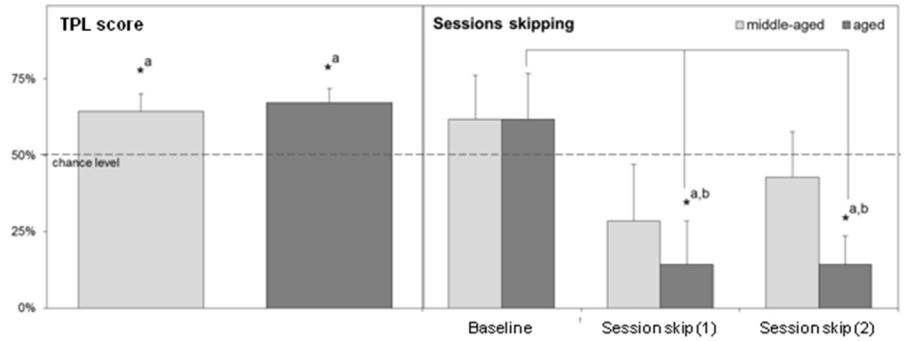


FIGURE 4 | Left: Average TPL performance in the 2-arm TPL setup of middle-aged and aged CD1 mice over the last 10 days of testing. **Right:** Performance after two separate morning session (session 1) skips measured in the second session. For statistical comparison, a "baseline" of second session performance around the time of the session skips is also shown. Sessions were skipped on days 15 and 17. The baseline consists of average performances in session 2 on days 13, 14 and 16. Chance level is indicated by the horizontal dotted line in both figures. Error bars represent SEM. Significant differences (*$p < 0.05$) with chance level are indicated by superscript "a"; significant differences with baseline are indicated by superscript "b".

test day, at the time of their first (batch 2) or second (batch 1) daily test session, together with HCC mice. All mice had been similarly food deprived (see "Materials and Methods" Section for more details). CD1 mice were not studied because (a) none of the CD1 mice mastered the 3-arm TPL task and (b) CD1 mice mastering the 2-arm TPL task did not use a circadian but instead an ordinal (non-circadian) strategy. Likewise aged C57Bl/6 mice are unable to master the 3-arm TPL task, unless they were trained in this task earlier in their life (Mulder et al., 2015).

Representative pictures of the immunostainings of TPL-trained mice are shown in **Figure 6**. Cry-2 immunoreactivity was found in the nuclei of neurons, mainly located in the SCN and surrounding brain regions (see **Figure 6A**), and the DG of the hippocampus (see **Figure 6D**). pCREB-immunoreactivity, also present in neuronal nuclei, was most strongly expressed in the DG of the hippocampus (see **Figure 6E**), whereas AVP-immunoreactivity present in the cytoplasm of neurons was found most strongly in regions of the hypothalamus, including the SCN as shown previously with this antibody (Van der Zee and Bult, 1995; see **Figure 6C**). c-Fos-immunoreactivity was present throughout the brain, including the SCN (**Figure 6B**), the DG of the hippocampus (**Figure 6F**), and the PVT (**Figure 6G**).

(Semi)-quantitative results of the different immunostainings are summarized in **Figure 7**. Because different quantification methods were used, all results are expressed as percentage relative to the HCC group (set at 100% expression) for optimal comparison. In the SCN we analyzed c-Fos, CRY2 and AVP, and in the hippocampus we analyzed CRY2, c-Fos and pCREB in those subregions where specific and clear immunostaining was present. pCREB was also analyzed in the cortex for its function in the storage of long-term memory. C-Fos was additionally analyzed in the (anterior) PVT, because a clear signal (specific staining of neurons) was observed. No differences were found between TPL-trained and HCC mice at the level of the SCN for the investigated

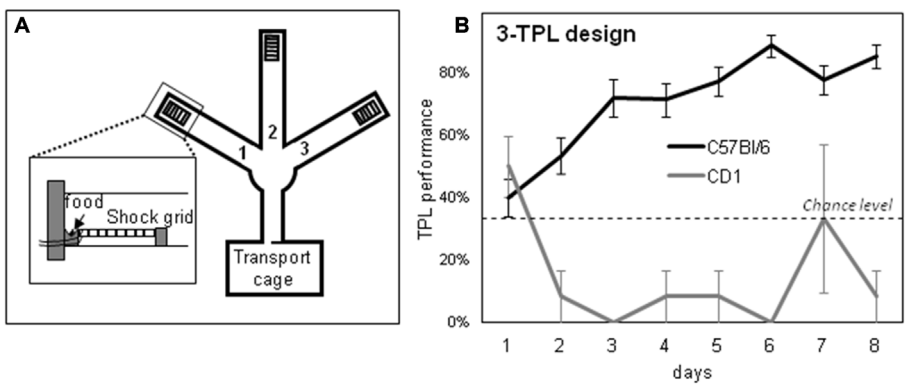


FIGURE 5 | A schematic representation of the 3-arm TPL test apparatus (A) and the learning curve of young C57Bl/6 mice (B; C57Bl/6 mice gradually mastered the task). Chance level is at 33%. The inset in **(A)** shows the shock grid and food location at the end of an arm. In a target arm, no footshock is delivered, whereas in a non-target arm food and footshock delivery are combined.

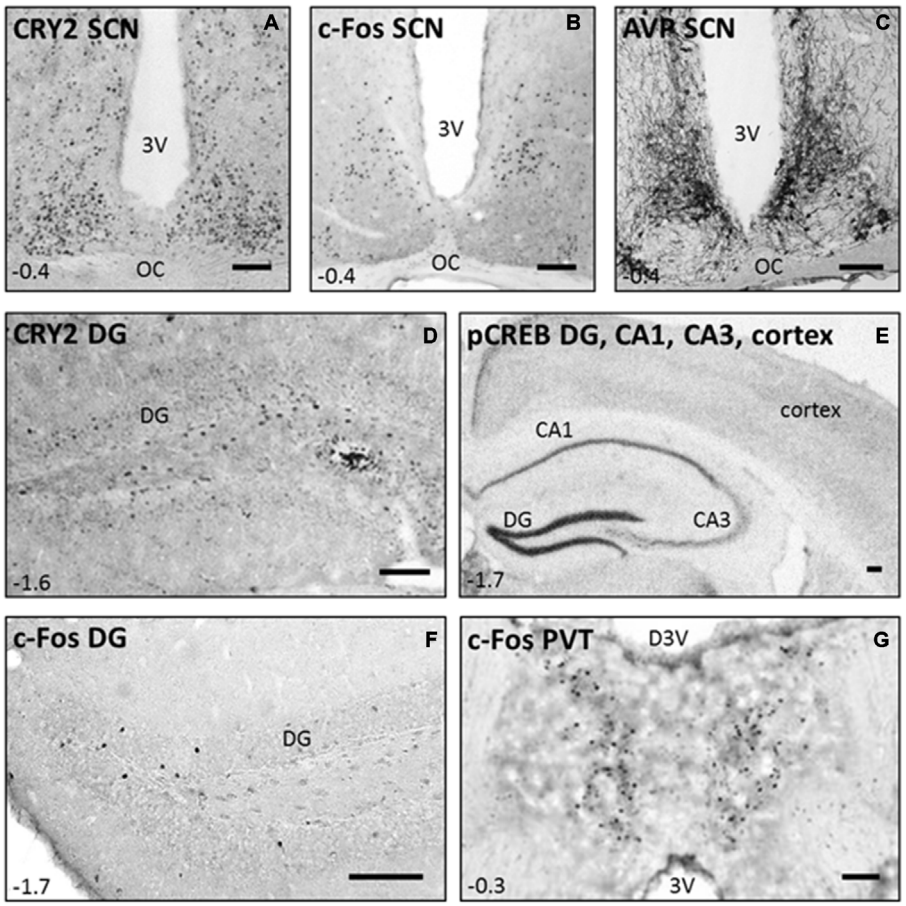


FIGURE 6 | Immunostainings performed in C57Bl/6 mice after they successfully mastered the 3-arm TPL task. Representative pictures of CRY2, c-Fos, and AVP immunoreactivity in the suprachiasmatic nucleus (SCN; **A–C**), CRY2 in the DG (**D**, CA3 not shown), pCREB in the DG, CA1, CA3 and cortex **(E)**, and c-Fos in the DG and paraventricular nucleus (PVT; **F,G**). Coordinates relative to bregma are shown in the left lower corner of each panel (according to the mouse brain atlas: Franklin and Paxinos, 1997). Scale bars in the right lower corner of each panel indicate 100 μm in all panels. 3 V = third ventricle; OC = Optic Chiasm; D3 V = dorsal third ventricle.

markers. This is in line with our earlier finding that the SCN is not essential for TPL (Mulder et al., 2014). Notably, a significant decrease in c-Fos positive cell-counts were found in the PVT and in the DG. The optical density of pCREB-positive cells located in DG, CA1, CA3 and Somatosensory Barrel Cortex was found to be significantly decreased in TPL-trained mice compared to HCC mice. In contrast, CRY2 immunoreactivity showed a 26% increase in the DG of TPL-trained mice compared to HCC mice (Cohen's $d = 0.89$; effect-size $r = 0.41$), which was at the border of significance ($p = 0.09$).

DISCUSSION

Here, we studied CD1 mice in the TPL paradigm (first aim of the study) and showed that the CD1 mouse, which is relatively poor in hippocampal functioning and ages relatively fast, cannot master the 3-arm TPL task. They can master the 2-arm TPL task, but middle-aged and notably aged CD1 mice use an ordinal (non-circadian) strategy. This strategy most likely depends on the striatum (they learned a sequence of events) instead of a circadian strategy by which they use their circadian system as a timing device (in the latter case referred to as cTPL). These results further stress the aging-sensitivity of TPL, and are in support of hippocampal involvement in cTPL performance. Thereafter, we set out to identify (parts of) the neuronal substrate underlying successful TPL performance (second aim of the study) by way of IHC analyses of CRY2, c-Fos, AVP and pCREB in brain sections of C57Bl/6 mice that mastered the 3-arm TPL task. The hippocampus showed significant changes for c-Fos and pCREB, further indicating a role of the hippocampus in mastering cTPL. An increased expression of CRY2 by 26% in the DG fits the earlier observation that the 3-arm TPL task is Cry-dependent (Van der Zee et al., 2008). Of interest is the strong change in c-Fos expression in the PVT, a circadian relay station in the thalamus (Moga et al., 1995).

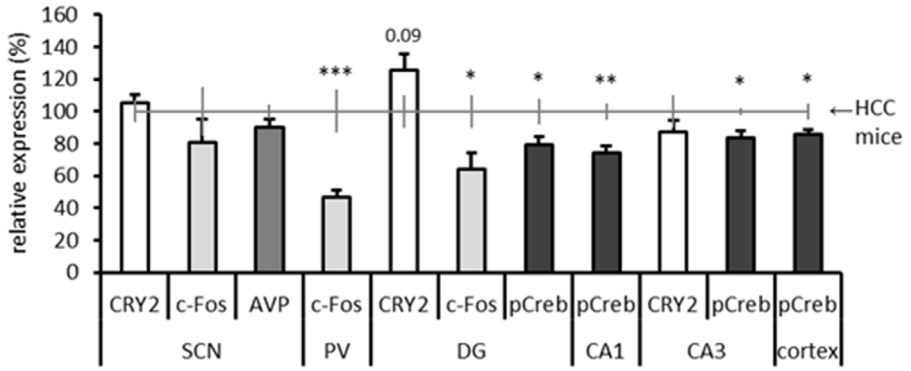


FIGURE 7 | Summary of results of all performed immunostainings in investigated brain regions. Expression levels are relative to home cage control (HCC) mice, which are depicted by the horizontal gray line at 100% (including error bars). The Dentate gyrus (DG), Cornu Ammonis areas 1 and 3 (CA1; CA3) are subregions of the hippocampus. Same markers are indicated by same grayscale colors. All error bars represent SEM. Statistical evaluations (two-tailed unpaired *t*-tests) of expression in HCC vs. TPL trained mice are included: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. CRY2 expression in the DG showed a statistical trend toward significance ($p = 0.09$).

TPL and Aging

An important step to studying TPL behavior in laboratory settings has been the development of a suitable paradigm, in which animals show consistent cTPL behavior. Recently, we reviewed the long road towards such a functional paradigm (Mulder et al., 2013a). The key has been to find a balanced approach between a reward to motivate animals to choose correct locations (finding food while hungry), in combination with a punishment (response cost) for choosing incorrect locations. Note that a response cost is likely implicit in widespread natural habitats, because traveling to a non-rewarding/predated location will (at best) be costly on energy. Scaling down TPL behavior into a laboratory setting therefore required the artificial implementation of such a response cost, which we have done so by the application of a mild but aversive footshock.

Previously, we investigated TPL for the first time in the context of aging (Mulder et al., 2015). We found that most untrained C57Bl/6 mice were unable to acquire TPL at middle-age (17 months). Surprisingly, some mice did master the task by adapting an alternative (ordinal) TPL strategy. We hypothesize that age-related hippocampal dysfunction, together with age-related circadian system decline caused these untrained mice to adapt this ordinal (non-circadian) TPL strategy, which is presumably less cognitively demanding than cTPL (Mulder et al., 2013a). In contrast, mice trained over their lifespan successfully maintained the circadian strategy (cTPL, learned at young age) until old age (Mulder et al., 2015). At this age however, mice showed signs of behavioral rigidity and a lack to update TOD information. The aging-sensitivity of the TPL paradigm was further stressed by the failure of middle-aged CD1 mice (in contrast to middle-aged C57Bl/6 mice) to master the 3-arm TPL task. It remains to be determined, however, whether young CD1 mice can master this task. An overview of the previously obtained results and the currently obtained results are shown in **Table 2**.

The striatum and hippocampus are widely held to be components of distinct memory systems that can guide competing behavioral strategies (Berke et al., 2009; Hagewoud et al., 2010). While hippocampus-dependent episodic memory is particularly age sensitive, the striatal system is more age-resistant (Churchill et al., 2003; Nilsson, 2003). We suggest that (c)TPL requires the plasticity of an intact hippocampus (hippocampal-driven strategy), while ordinal TPL, as used by aged mice in general and CD1 mice in particular, may instead rely more on the aging-resistant striatal (procedural; striatal-driven strategy) memory system. This hypothesis may be confirmed in future studies, for instance by selective lesions in the hippocampus and striatum. To what extent the striatum is involved in (c)TPL is currently unknown and requires future experiments.

The Neuronal Substrate of TPL

Here, we applied IHC on the brains of young to middle-aged C57Bl6/J mice that had successfully mastered cTPL. These mice were sacrificed the day after their last TPL test day on a test-session time point, together with HCC mice. We investigated the expression of vasopressin (AVP, the main circadian output of the SCN), CRY2, and a plasticity marker (pCREB) in the SCN, but we found no differences compared to HCC mice. This corroborates with our SCN lesion results which have indicated that the SCN is not the primary clock used in cTPL (Mulder et al., 2014). The current findings do not support a modulating role of the SCN in TPL. Perhaps other markers should be investigated. Gritton et al. showed that cholinergic signaling from the basal forebrain to the SCN can serve as a temporal timestamp attenuating SCN photic-driven rhythms during cognitive training (Gritton et al., 2013). Cholinergic markers may thus be interesting to further investigate this putative SCN gating mechanism. Noteworthy, in contrast to rats, the SCN in mice does not contain cholinergic neurons, but the SCN of both species do express cholinergic receptors extensively (Van der Zee et al., 1991; Hut and Van der Zee, 2011).

TABLE 2 | Overview of previous and current findings.

	C57Bl/6 mice		CD1 mice	
Age	**Young/Middle aged**	**Aged/Old**	**Young/Middle aged**	**Aged/Old**
2-arm TPL	n.d.	n.d.	**Successful**	**Successful**
			Use ordinal strategy	**Use ordinal strategy**
3-arm TPL	*Successful*	*Fail*	**Fail**	**Fail**
	Use circadian strategy	Some use ordinal strategy	**No strategy**	**No strategy**
	IHC analyses			
Spontaneous alternation scores	*Ca. 70%*	*Ca. 70%*	**Ca. 50%**	**Ca. 50%**
Circadian system	*intact*	*Age deteriorated*	**intact**	**Age deteriorated**
Cross maze	**No preference**	**Mainly hippocampal**	**Mainly striatal**	**striatal**

A summary of the previous findings (in italic; see also Mulder et al., 2015) and the current findings (in bold). Analyses of the neuronal substrate by way of immunohistochemistry (IHC) has been limited to young and middle-aged C57Bl/6 mice that mastered cTPL successfully in the 3-arm TPL set up. n.d. = not determined.

We showed that the most pronounced difference between TPL trained and HCC mice was found in c-Fos expression in the PVT, which has been referred to as a circadian system relay station (Moga et al., 1995). The PVT receives input from all major components of the circadian timing system, including the SCN, subparaventricular zone, the intergeniculate leaflet, and the retina. In addition, the PVT is connected to brain areas involved in learning and memory, including the ventral striatum, amygdala, entorhinal cortex, hippocampus, and cortex (Pickard, 1982; Watts et al., 1987; Moga et al., 1995). The PVT may thus be an interesting target area for future lesion studies in the context of cTPL.

Notably, a significant decrease in c-Fos positive cell-count in the DG and the optical density of pCREB-positive cells located in DG, CA1, CA3 and Somatosensory Barrel Cortex was found in TPL trained mice compared to HCC mice. One explanation for these decreased expression levels is that mice were extensively trained. It has been shown that, with extensive training, c-Fos is attenuated in most brain regions (Bertaina-Anglade et al., 2000). Moreover, c-Fos and pCREB are related as pCREB stimulates the expression of c-Fos (Sheng and Greenberg, 1990). In extensively trained animals, the hippocampus may be devoted to the learned task (retention rather than acquisition) activating only the cells devoted to this task. From another perspective, training may increase synchronization of hippocampal neurons, causing less cells to be active at one given time point. It would therefore be interesting to also investigate these markers during the learning (acquisition) phase of TPL. Kononen et al. (1990) showed that in the rat brain, c-Fos levels show a circadian rhythmicity, with peak expression in the active (dark) phase. Therefore, another explanation for the decreased expression levels may be that TPL testing induced a phase shift (advance) in c-Fos (and pCREB) circadian expression relative to the "normal" expression pattern in HCC mice.

The 26% upregulation of CRY2 in the DG of TPL-trained mice compared to HCC mice is an interesting finding. cTPL likely involves the hippocampus, which is known to be involved in spatial navigation and episodic and episodic-like memory. The DG is one of the few brain areas where adult neurogenesis occurs, and thought to be particularly involved in the formation of new episodic memories (Amaral et al., 2007; Treves et al., 2008). It has been proposed that experience-related cues (cognitive training) may act as a zeitgeber to the hippocampus, where local timekeeping mechanisms may be entrained (Gritton et al., 2013). Whether *Cry*, but not *Per* genes are essential for temporal coding in the hippocampus remains to be further investigated, for example by using hippocampus specific *Cry* and *Per* knockout mice.

TPL as a Model for Episodic-Like Memory

Numerous clinical studies have established a direct correlation between abnormal circadian clock functions and the severity of neurodegenerative disorders, suggesting a functional link between the circadian clock and age-associated decline of brain functions (Kondratova and Kondratov, 2012). cTPL demonstrates that animals can form so-called "tripartite memory codes" consisting of associated what, where, and when information, resembling the content of human episodic memory. This type of hippocampus-dependent memory is particularly susceptible to the pathologies of aging and neurodegenerative disease (Squire et al., 2004; Stranahan et al., 2008; Berke et al., 2009). Therefore, TPL may have specific potential as an animal model for episodic memory and aging. It has been demonstrated that rats and mice are able to associate object-, spatial-, and temporal information after a single exposure to such stimulus constellations (Dere et al., 2005a,b, 2007). Hence, the first trials of cTPL training are potentially episodic-like in nature, and link cTPL to episodic-like memory. Behavioral models based on temporal information are scarce, yet essential to test interventions that potentially improve detrimental effects of aging and (episodic) memory related diseases like Alzheimer's disease (AD; Dere et al., 2005a,b). Indeed, patients suffering from AD are often said to be disorientated in time and place, and memories of when and where things happened (episodic memory) are among the first to be affected in AD patients. Aging is characterized by cognitive decline (Winocur, 1992; Nilsson, 2003; Hedden and Gabrieli, 2004; Burke and Barnes, 2006), as well as circadian system deterioration (Turek et al., 1995; Van der Zee et al., 1999; Hofman and Swaab, 2006; Brown et al., 2011; Kondratova and Kondratov, 2012).

We therefore predicted that cTPL is specifically age sensitive, as shown in this study and earlier work (Mulder et al., 2015).

Whether and to what extent the (c)TPL task is an episodic-like type of memory paradigm remains a matter of debate. Taken the seven criteria of Pause et al. (2013), it does not fulfill the criteria as rehearsal is a critical aspect of TPL. Nevertheless, the task requires integrated what–where–when components, 24 h-retention, relies on the hippocampus and is sensitive to aging. Moreover cTPL requires specific knowledge of TOD rather than a discrimination of relative recency, as in most other episodic memory paradigms. For these reasons (c)TPL can significantly contribute to our understanding of mechanisms underlying episodic-like memory or specific temporal aspects of episodic-like memory. The TPL task could be viewed as a collection of multiple episodic memories, and/or a semantic memory task using specific episodic information. Moreover, it may shed light on the way TOD information is encoded into memory. Similarly humans can often remember the TOD of specific events within the range of some hours (a significant event happened in the early or late morning, for example). Interestingly, also in cTPL mice remember the TOD within a range of approximately 1.5 h (Mulder et al., 2013a, 2015). The existence of circadian-timed episodic-like memory has also been claimed in other species, such as bees (Pahl et al., 2007). Taken together, TPL and particularly cTPL can functionally be linked to episodic-like memory even if the task seems more related to semantic memory due to the repeated trials needed to successfully master the task. We suspect that TPL depends on episodic memory, but due to its functional nature, also entail the translation of experienced episodes into semantic rules acquired by training. A next step would be to directly compare underlying neuronal substrates in an established episodic-like memory task and cTPL.

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REFERENCES

Amaral, D. G., Scharfman, H. E., and Lavenex, P. (2007). The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Prog. Brain Res.* 163, 3–22. doi: 10.1016/s0079-6123(07)63001-5

Begega, A., Cienfuegos, S., Rubio, S., Santin, J. L., Miranda, R., Arias, J. L., et al. (2001). Effects of ageing on allocentric and egocentric spatial strategies in the Wistar rat. *Behav. Processes* 53, 75–85. doi: 10.1016/s0376-6357(00)00150-9

Berke, J. D., Breck, J. T., and Eichenbaum, H. (2009). Striatal versus hippocampal representations during win-stay maze performance. *J. Neurophysiol.* 101, 1575–1587. doi: 10.3410/f.1167958.630058

Bernabeu, R., Bevilaqua, L., Ardenghi, P., Bromberg, E., Schmitz, P., Bianchin, M., et al. (1997). Involvement of hippocampal cAMP/cAMP-dependent protein kinase signaling pathways in a late memory consolidation phase of aversively motivated learning in rats. *Proc. Natl. Acad. Sci, U.S.A.* 94, 7041–7046. doi: 10.1073/pnas.94.13.7041

Bertaina-Anglade, V., Tramu, G., and Destrade, C. (2000). Differential learning-stage dependent patterns of c-Fos protein expression in brain regions during the acquisition and memory consolidation of an operant task in mice. *Eur. J. Neurosci.* 12, 3803–3812. doi: 10.1046/j.1460-9568.2000.00258.x

Biemans, B. A., Van der Zee, E. A., and Daan, S. (2003). Age-dependent effects of conditioning on cholinergic and vasopressin systems in the rat suprachiasmatic nucleus. *Biol. Chem.* 384, 729–736. doi: 10.1515/bc.2003.081

Binder, S., Dere, E., and Zlomuzica, A. (2015). A critical appraisal of the what–where–when episodic-like memory test in rodents: Achievements, caveats and future directions. *Prog. Neuroibiol.* 130, 71–85. doi: 10.1016/j.pneurobio.2015.04.002

Brown, S. A., Pagani, L., Cajochen, C., and Eckert, A. (2011). Systemic and cellular reflections on ageing and the circadian oscillator: a mini-review. *Gerontology* 57, 427–434. doi: 10.1159/000320673

Bult, A., Van der Zee, E. A., Compaan, J. C., and Lynch, C. B. (1992). Differences in the number of arginine-vasopressin-immunoreactive neurons exist in the suprachiasmatic nuclei of house mice selected for differences in nest-building behavior. *Brain Res.* 578, 335–338. doi: 10.1016/0006-8993(92)90266-c

Burke, S. N., and Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nat. Rev. Neurosci.* 7, 30–40. doi: 10.1038/nrn1809

Chia, R., Achilli, F., Festing, M. F. W., and Fisher, E. M. C. (2005). The origins and uses of mouse outbred stocks. *Nat. Genet.* 37, 1181–1186. doi: 10.1038/ng1665

Churchill, J. D., Stanis, J. J., Press, C., Kushelev, M., and Greenough, W. T. (2003). Is procedural memory relatively spared from age effects? *Neurobiol. Aging.* 24, 883–892. doi: 10.1016/s0197-4580(02)00194-x

Colombo, P. J., Brightwell, J. J., and Countryman, R. A. (2003). Cognitive strategy-specific increases in phosphorylated cAMP response element-binding protein and c-Fos in the hippocampus and dorsal striatum. *J. Neurosci.* 23, 3547–3554.

Countryman, R. A., Orlowski, J. D., Brightwell, J. J., Oskowitz, A. Z., and Colombo, P. J. (2005). CREB phosphorylation and c-Fos expression in the hippocampus of rats during acquisition and recall of a socially transmitted food preference. *Hippocampus* 15, 56–67. doi: 10.1002/hipo.20030

Dere, E., Huston, J. P., and Souza Silva, M. A. (2005a). Episodic-like memory in mice: simultaneous assessment of object, place and temporal order memory. *Brain Res. Protoc.* 16, 10–19. doi: 10.1016/j.brainresprot.2005.08.001

Dere, E., Huston, J. P., and Souza Silva, M. A. (2005b). Integrated memory for objects, places and temporal order: evidence for episodic-like memory in mice. *Neurobiol. Learn. Mem.* 84, 214–221. doi: 10.1016/j.nlm.2005.07.002

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2007). The pharmacology, neuroanatomy and neurogenesis of one-trial object recognition in rodents. *Neurosci. Biobehav. Rev.* 31, 673–704. doi: 10.1016/j.neubiorev.2007.01.005

Franklin, K. B. J., and Paxinos, G. (1997). *The Mouse Brain in Stereotaxic Coordinates*, 2nd Edn. San Diego, CA: Academic Press, 264.

Gage, F. H. (2002). Neurogenesis in the adult brain. *J. Neurosci.* 22, 612–613.

Gerkema, M. P., Van der Zee, E. A., and Feitsma, L. E. (1994). Expression of circadian rhythmicity correlates with the number of arginine-vasopressine-immunoreactive cells in the suprachiasmatic nucleus of common voles, Microtus arvalis. *Brain Res.* 639, 93–101. doi: 10.1016/0006-8993(94)91768-x

Gil-Mohapel, J., Brocardo, P. S., Choquette, W., Gothard, R., Simpson, J. M., and Christie, B. R. (2013). Hippocampal neurogenesis levels predict watermaze search strategies in the aging brain. *PLoS One* 8:e75125 doi: 10.1371/journal.pone.0075125

Gritton, H. J., Stasiak, A. M., Sarter, M., and Lee, T. M. (2013). Cognitive performance as a zeitgeber: cognitive oscillators and cholinergic modulation of the SCN entrain circadian rhythms. *PLoS One* 8:e56206. doi: 10.3410/f.718376861.793494795

Guzowski, J. F., and McGaugh, J. L. (1997). Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc. Natl. Acad. Sci. U S A* 94, 2693–2698. doi: 10.1073/pnas.94.6.2693

Hagewoud, R., Havekes, R., Tiba, P. A., Novati, A., Hogenelst, K., Weinreder, P., et al. (2010). Coping with sleep deprivation: shifts in regional brain activity and learning strategy. *Sleep* 33, 1465–1473.

Havekes, R., Abel, T., and Van der Zee, E. A. (2011). The cholinergic system and neostriatal functions. *Behav. Brain Res.* 221, 412–423. doi: 10.1016/j.bbr.2010.11.047

Hedden, T., and Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat. Rev. Neurosci.* 5, 87–96. doi: 10.1038/nrn1323

Hofman, M. A., and Swaab, D. F. (2006). Living by the clock: the circadian pacemaker in older people. *Ageing Res. Rev.* 5, 33–51. doi: 10.1016/j.arr.2005.07.001

Hut, R. A., and Van der Zee, E. A. (2011). The cholinergic system, circadian rhythmicity and time memory. *Behav. Brain Res.* 221, 466–480. doi: 10.1016/j.bbr.2010.11.039

Johnson, M. (2014). Laboratory Mice and Rats. *Mater. Methods* 2: 113. doi: 10.5962/bhl.title.65460

Kalamatianos, T., Kallo, I., and Coen, C. W. (2004). Ageing and the diurnal expression of the mRNAs for vasopressin and for the V1a and V1b vasopressin receptors in the suprachiasmatic nucleus of male rats. *J. Neuroendocrinol.* 16, 493–501. doi: 10.1111/j.1365-2826.2004.01196.x

Kalsbeek, A., Fliers, E., Hofman, M. A., Swaab, D. F., and Buijs, R. M. (2010). Vasopressin and the output of the hypothalamic biological clock. *J. Neuroendocrinol.* 22, 362–372. doi: 10.1111/j.1365-2826.2010.01956.x

Kawashima, T., Okuno, H., and Bito, H. (2014). A new era for functional labeling of neurons: activity-dependent promoters have come of age. *Front. Neural Circuits* 8:37. doi: 10.3389/fncir.2014.00037

Kempermann, G., Kuhn, H. G., and Gage, F. H. (1997). Genetic influence on neurogenesis in the dentate gyrus of adult mice. *Proc. Natl. Acad. Sci. U.S.A.* 94, 10409–10414. doi: 10.1073/pnas.94.19.10409

Kondratova, A. A., and Kondratov, R. V. (2012). The circadian clock and pathology of the ageing brain. *Nat. Rev. Neurosci.* 13, 325–335. doi: 10.1038/nrn3208

Kononen, J., Koistinaho, J., and Alho, H. (1990). Circadian rhythm in c-fos-like immunoreactivity in the rat brain. *Neurosci. Lett.* 120, 105–108. doi: 10.1016/0304-3940(90)90179-d

Kuhn, H. G., Dickinson-Anson, H., and Gage, F. H. (1996). Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J. Neurosci.* 16, 2027–2033.

Lamprecht, R., Hazvi, S., and Dudai, Y. (1997). cAMP response element-binding protein in the amygdala is required for long- but not short-term conditioned taste aversion memory. *J. Neurosci.* 17, 8443–8450.

Moga, M. M., Weis, R. P., and Moore, R. Y. (1995). Efferent projections of the paraventricular thalamic nucleus in the rat. *J. Comp. Neurol.* 359, 221–238. doi: 10.1002/cne.903590204

Morgan, J. I., Cohen, D. R., Hempstead, J. L., and Curran, T. (1987). Mapping patterns of c-fos expression in the central nervous system after seizure. *Science* 237, 192–197. doi: 10.1126/science.3037702

Mulder, C. K., Gerkema, M. P., and Van der Zee, E. A. (2013a). Circadian clocks and memory: time place learning. *Front. Mol. Neurosci.* 6:8. doi: 10.3389/fnmol.2013.00008

Mulder, C., Van der Zee, E. A., Hut, R. A., and Gerkema, M. P. (2013b). Time-place learning and memory persist in mice lacking functional per1 and per2 clock genes. *J. Biol. Rhyhms* 28, 367–379. doi: 10.1177/0748730413512958

Mulder, C. K., Papantoniou, C., Gerkema, M. P., and Van der Zee, E. A. (2014). Neither the SCN nor the adrenals are required for circadian time-place learning in mice. *Chronobiol. Int.* 31, 1075–1092. doi: 10.3109/07420528.2014.944975

Mulder, C. K., Reckman, G. A., Gerkema, M. P., and Van der Zee, E. A. (2015). Time-place learning over a lifetime: absence of memory loss in trained old mice. *Learn. Mem.* 22, 278–288. doi: 10.1101/lm.037440.114

Nilsson, L. G. (2003). Memory function in normal aging. *Acta Neurol. Scand. Suppl.* 179, 7–13. doi: 10.1034/j.1600-0404.107.s179.5.x

Pahl, M., Zhu, H., Pix, W., Tautz, J., and Zhang, S. (2007). Circadian timed episodic-like memory - a bee knows what to do when and also where. *J. Expt. Biol.* 210, 3559–3567. doi: 10.1242/jeb.005488

Patil, S. S., Li, K., Heo, S., Hoger, H., and Lubec, G. (2012). Proteins linked to spatial memory formation of CD1 mice in the multiple T-maze. *Hippocampus* 22, 1075–1086. doi: 10.1002/hipo.20956

Pause, B. M., Zlomuzica, A., Kinugawa, K., Mariani, J., Pietrowsky, R., and and Dere, E. (2013). Perspectives on episodic-like and episodic memory. *Front. Behav. Neurosci.* 7:33. doi: 10.3389/fnbeh.2013.00033

Pickard, G. E. (1982). The afferent connections of the suprachiasmatic nucleus of the golden hamster with emphasis on the retinohypothalamic projection. *J. Comp. Neurol.* 211, 65–83. doi: 10.1002/cne.902110107

Sagar, S. M., Sharp, F. R., and Curran, T. (1988). Expression of c-fos protein in brain: metabolic mapping at the cellular level. *Science* 240, 1328–1331. doi: 10.1126/science.3131879

Sheng, M., and Greenberg, M. E. (1990). The regulation and function of c-fos and other immediate early genes in the nervous system. *Neuron* 4, 477–485. doi: 10.1016/0896-6273(90)90106-p

Smarr, B. L., Jennings, K. J., Driscoll, J. R., and & Kriegsfeld, L. J. (2014). A Time to Remember: The Role of Circadian Clocks in Learning and Memory. *Behav. Neurosci.* 128, 283–303. doi: 10.1037/a0035963

Squire, L. R., Stark, C. E., and Clark, R. E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306. doi: 10.1146/annurev.neuro.27.070203.144130

Stranahan, A. M., Lee, K., and Mattson, M. P. (2008). Contributions of impaired hippocampal plasticity and neurodegeneration to age-related deficits in hormonal pulsatility. *Ageing Res. Rev.* 7, 164–176. doi: 10.1016/j.arr.2007.12.004

Treves, A., Tashiro, A., Witter, M. P., and Moser, E. I. (2008). What is the mammalian dentate gyrus good for? *Neuroscience* 154, 1155–1172. doi: 10.1016/j.neuroscience.2008.04.073

Turek, F. W., Penev, P., Zhang, Y., van Reeth, O., and Zee, P. (1995). Effects of age on the circadian system. *Neurosci. Biobehav. Rev.* 19, 53–58. doi: 10.1016/0149-7634(94)00030-5

Van der Borght, K., Havekes, R., Bos, T., Eggen, B. J., and Van der Zee, E. A. (2007). Exercise improves memory acquisition and retrieval in the Y-maze task: relationship with hippocampal neurogenesis. *Behav. Neurosci.* 121, 324–334. doi: 10.1037/0735-7044.121.2.324

van der Veen, D. R., Mulder, E. G., Oster, H., Gerkema, M. P., and Hut, R. A. (2008). SCN-AVP release of mPer1/mPer2 double-mutant mice *in vitro*. *J. Circadian Rhythms* 6, 5. doi: 10.1186/1740-3391-6-5

Van der Zee, E. A. (2015). Synapses, spines and kinases in mammalian learning and memory and the impact of aging. *Neurosci. Biobehav. Rev.* 50, 77–85. doi: 10.1016/j.neubiorev.2014.06.012

Van der Zee, E. A., Biemans, B. A., Gerkema, M. P., and Daan, S. (2004). Habituation to a test apparatus during associative learning is sufficient to enhance muscarinic acetylcholine receptor-immunoreactivity in rat suprachiasmatic nucleus. *J. Neurosci. Res.* 78, 508–519. doi: 10.1002/jnr.20300

Van der Zee, E. A., Havekes, R. A., Barf, R. P., Hut, R. A., Nijholt, I. M., Jacobs, E. H., et al. (2008). Circadian time-place learning in mice depends on Cry genes. *Curr. Biol.* 18, 844–848. doi: 10.1016/j.cub.2008.04.077

Van der Zee, E. A., Jansen, K., and Gerkema, M. P. (1999). Severe loss of vasopressin-immunoreactive cells in the suprachiasmatic nucleus of aging voles coincides with reduced circadian organization of running wheel activity. *Brain Res.* 816, 572–579. doi: 10.1016/s0006-8993(98)01239-6

Van der Zee, E. A., Boersma, G. J., and Hut, R. A. (2009). The neurobiology of circadian rhythms. *Curr. Opin. Pulm. Med.* 15, 534–539. doi: 10.1097/MCP.0b013e3283319b29.

Van der Zee, E. A., and Bult, A. (1995). Distribution of AVP and Ca^{2+}-dependent PKC-isozymes in the suprachiasmatic nucleus of the mouse and rabbit. *Brain Res.* 701, 99–107. doi: 10.1016/0006-8993(95)00968-1

Van der Zee, E. A., Streefland, C., Strosberg, A. D., Schröder, H., and Luiten, P. G. (1991). Colocalization of muscarinic and nicotinic receptors in cholinoceptive neurons of the suprachiasmatic nucleus in young and aged rats. *Brain Res.* 542, 348–352. doi: 10.1016/0006-8993(91)91590-w

van Praag, H., Shubert, T., Zhao, C., and Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* 25, 8680–8685. doi: 10.1523/jneurosci.1731-05.2005

Watts, A. G., Swanson, L. W., and Sanchez-Watts, G. (1987). Efferent projections of the suprachiasmatic nucleus: I. Studies using anterograde transport of Phaseolus vulgaris leucoagglutinin in the rat. *J. Comp. Neurol.* 258, 204–229. doi: 10.1002/cne.902580204

Winocur, G. (1992). Conditional learning in aged rats: evidence of hippocampal and prefrontal cortex impairment. *Neurobiol. Aging* 13, 131–135. doi: 10.1016/0197-4580(92)90020-x

Yamamoto, N., and Degirolamo, G. J. (2012). Differential effects of aging on spatial learning through exploratory navigation and map reading. *Front. Aging Neurosci.* 4:14. doi: 10.3389/fnagi.2012.00014

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Autobiographical memory: a clinical perspective

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Autobiographical memory (ABM) comprises memories of one's own past that are characterized by a sense of subjective time and autonoetic awareness. Although ABM deficits are among the primary symptoms of patients with major psychiatric conditions such as mild cognitive impairment (MCI) and Alzheimer Disease (AD) or chronic schizophrenia large clinical studies are scarce. We therefore summarize and discuss the results of our clinical studies on ABM deficits in the respective conditions. In these studies ABM was assessed by using the same instrument – i.e., the Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI) – thus allowing a direct comparison between diagnostic groups. Episodic ABM, especially the richness of details was impaired already in MCI and in beginning AD. Semantic memories were spared until moderate stages, indicating a dissociation between both memory systems. A recency effect was detectable in cognitively unimpaired subjects and vanished in patients with AD. A similar pattern of deficits was found in patients with chronic schizophrenia but not in patients with major depression. These ABM deficits were not accounted for by gender, or education level and did not apply for the physiological ageing process in otherwise healthy elderly. In conclusion, ABM deficits are frequently found in AD and chronic schizophrenia and primarily involve episodic rather than semantic memories. This dissociation corresponds to the multiple trace theory which hypothesized that these memory functions refer to distinct neuronal systems. The semi-structured interview E-AGI used to discern ABM changes provided a sufficient reliability measures, moreover potential effects of a number of important confounders could be falsified so far. These findings underline the relevance of ABM-assessments in clinical practice.

Keywords: autobiographical memory, semantic memory, episodic memory, mild cognitive impairment, Alzheimer's disease, chronic schizophrenia, hippocampus, multiple trace theory

INTRODUCTION

Autobiographical memory (ABM) refers to memories of an individual, which are characterized by a sense of subjective time and autonoetic awareness (Tulving, 1972, 2002) and entailed by feelings of emotional re-experience (Tulving, 1983; Tulving and Markowitsch, 1998; Markowitsch, 2003). Because of the interaction of episodic and semantic memory and the uniqueness to humans ABM is considered to be crucial for the continuity of the self and the development of personal identity, i.e., processes which are typically disturbed in patients with major psychiatric conditions such as Alzheimer's disease (AD) or chronic schizophrenia (Conway and Pleydell-Pearce, 2000; Cuervo-Lombard et al., 2007; Berna et al., 2012; Seidl et al., 2011; Herold et al., 2013). As a part of the declarative memory, ABM comprises a semantic plus an episodic domain. While semantic ABM involves general facts from different life time periods, episodic ABM includes biographic events with a richness of details and a feeling of re-experiencing when recalled.

According to Ribot's law (Ribot, 1881) remote memories are more resistant to brain damage than recent one. Ribot's law stands in opposition to the recency effect that implies a better consolidation of recent memories than remote ones. Declarative mnestic deficits are among the core symptoms of AD and usually go along with anterograde memory impairment in the initial phases and loss of remote memory following Ribot's gradient in the more advanced stages (Sagar et al., 1988; Dall'Ora et al., 1989; Kopelman, 1989; Greene and Hodges, 1996; Dorrego et al., 1999; Piolino et al., 2003; Hou et al., 2005; Leyhe et al., 2009). Two important theoretical approaches regarding the role of the hippocampus on ABM retrieval are the standard model of consolidation and the multiple trace theory (Squire and Alvarez, 1995; Nadel and Moscovitch, 1997). The first approach suggests that the function of the hippocampus in ABM is time-limited; hence, memories become gradually independent of the medial temporal lobe (MTL) in the course of time. In contrast, the multiple trace theory predicts that the recall process of the episodic autobiographical memories requires the hippocampal formation irrespective of how old the relevant memories are. The semantic memories, however, could be recalled independently of this structure and were subject to Ribot's gradient. The majority of studies support the multiple trace theory (Conway et al., 1999; Piolino et al., 2004; Viard et al., 2007). There are also reports of spared personal-semantic memory but impaired personal episodic memories without a temporal gradient in patients with MTL lesions (Viskontas et al., 2000; Steinvorth et al., 2005; Noulhiane et al., 2008).

Autobiographical memory deficits are not specific to AD but were also described in mild cognitive impairment (MCI) and chronic schizophrenia. These changes do not only contribute to our understanding of the respective diseases but have the potential to facilitate clinical examination and diagnosis. However, the potential impact of important confounders, such as education, depressive mood, or the aging process as such needs to be addressed.

In the following we summarize and discuss findings from our studies on ABM deficits in MCI and AD, major depression, and chronic schizophrenia with reference to normal aging.

CLINICAL STUDIES

METHODS

Methodological details of the five studies conducted by our group as well as the description of sample characteristics are summarized in **Table 1**.

Autobiographical memory was investigated by using the Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI) (Kopelman et al., 1990; Fast et al., 2007) – a semi-structured autobiographical interview based on the ABM Interview of Kopelman and colleagues. A previous version of the E-AGI was used in one study. Both, personal-semantic facts (SEM) as well as free recalled

Table 1 | Studies on ABM in major depression, MCI, AD, and chronic schizophrenia.

Study	Psychometric instruments/ neuropsychological assessment/MRI	Subjects				
		Sample size	Patients' groups	Female/ male	Age (years): mean (SD)	Education (years): mean (SD)
Ahlsdorf (2009)	Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI), previous version	$N = 120$	Depression ($n = 30$)	21/9	68.8 (6.6)	11.8 (2.4)
	Mini mental state examination (MMSE)		MCI ($n = 30$)	15/15	70.2 (5.8)	12.3 (3.3)
	NEO five factor inventory (NEO-FFI)		AD ($n = 30$)	18/12	74.4 (6.7)	11.0 (2.7)
	Beck depression inventar (BDI)		Healthy controls ($n = 30$)	19/11	66.9 (5.9)	15.2 (3.3)
	Geriatric Depression Scale (GDS)					
	Apathy Evaluation Scale (self-rating)					
Seidl et al. (2011)	Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI)	$N = 239$	Patients with MCI ($n = 33$)	21/12	79.3 (6.9)	
	Global Deterioration Scale (GDS)		Patients with mild AD ($n = 35$)	26/9	84.3 (7.8)	
	Mini mental state examination (MMSE)		Patients with moderate AD ($n = 56$)	49/7	86.9 (6.1)	
	Neuropsychiatric inventory (NPI)		Patients with severe AD ($n = 74$)	64/10	87.1 (7.0)	
	Apathy Evaluation Scale (AES-10)		Healthy controls ($n = 41$)	25/16	76.0 (4.7)	
Berna et al. (2012)	Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI)	$N = 395$	MCI ($n = 63$)	29/34	74.0 (0.9)	12.3 (2.1)
	Nürnberger-Alters-Inventar (NAI)		Younger healthy controls ($n = 194$)	90/104	55.1 (1.0)	14.6 (2.5)
	Logical memory subtest (WMS-R)		Older healthy controls ($n = 138$)	73/65	73.8 (0.9)	13.9 (3.0)
	Trail Making Test, Versions A and B (TMT A, TMT B)					
Thomann et al. (2012)	Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI)	$N = 53$	MCI ($n = 15$)	8/7	73.3 (3.8)	12.3 (3.1)
	Mini mental state examination (MMSE)		Mild AD ($n = 14$)	7/7	73.7 (5.2)	11.4 (3.0)
	Magnetic resonance imaging (MRI)		Healthy controls ($n = 24$)	10/14	72.8 (3.3)	13.8 (3.6)
Herold et al. (2013)	Erweitertes Autobiographisches Gedächtnis Inventar (E-AGI)	$N = 54$	Schizophrenia ($n = 33$)	10/23	52.0 (8.8)	12.6 (2.8)
	Brief Psychiatric Rating Scale (BPRS)		Healthy controls ($n = 21$)	9/12	53.7 (8.0)	13.9 (2.1)
	Scale for the Assessment of Positive Symptoms (SAPS)					
	Scale for the Assessment of Negative Symptoms (SANS)					
	Apathy Evaluation Scale (AES)					
	Bielefelder Famous Faces Test (BFFT)					
	Magnetic resonance imaging (MRI)					

autobiographical events (EP-F) of five different lifetime periods (preschool, primary school, secondary school, early adulthood, recent 5 years) are considered. One autobiographical event from each lifetime period had to be described in detail. The score of maximal 11 points was given considering the number of details of such an event (EP-D). According to Conway (Conway, 1996; Conway and Pleydell-Pearce, 2000) event-specific knowledge plays a central role to autobiographical remembering and is stored and encoded in a completely different way than knowledge about "general events" or "lifetime periods," which can be assigned to semantic autobiographical knowledge. To reduce the time necessary for the examination and to consider the restrictions due to the psychiatric conditions, the interview was modified and limited to the following three lifetime periods (primary school, early adulthood, recent 5 years – **Figure 1**) in four studies.

STUDY 1: PSYCHOMETRIC PROPERTIES OF ABM ASSESSMENT AND EFFECTS OF DEPRESSED MOOD (AHLSDORF, 2009)

Group difference and effects of depressed mood

When compared between the four diagnostic groups, SEM scores showed only minor, non-significant differences. In contrast, EP-F scores were significantly higher in healthy controls, patients with

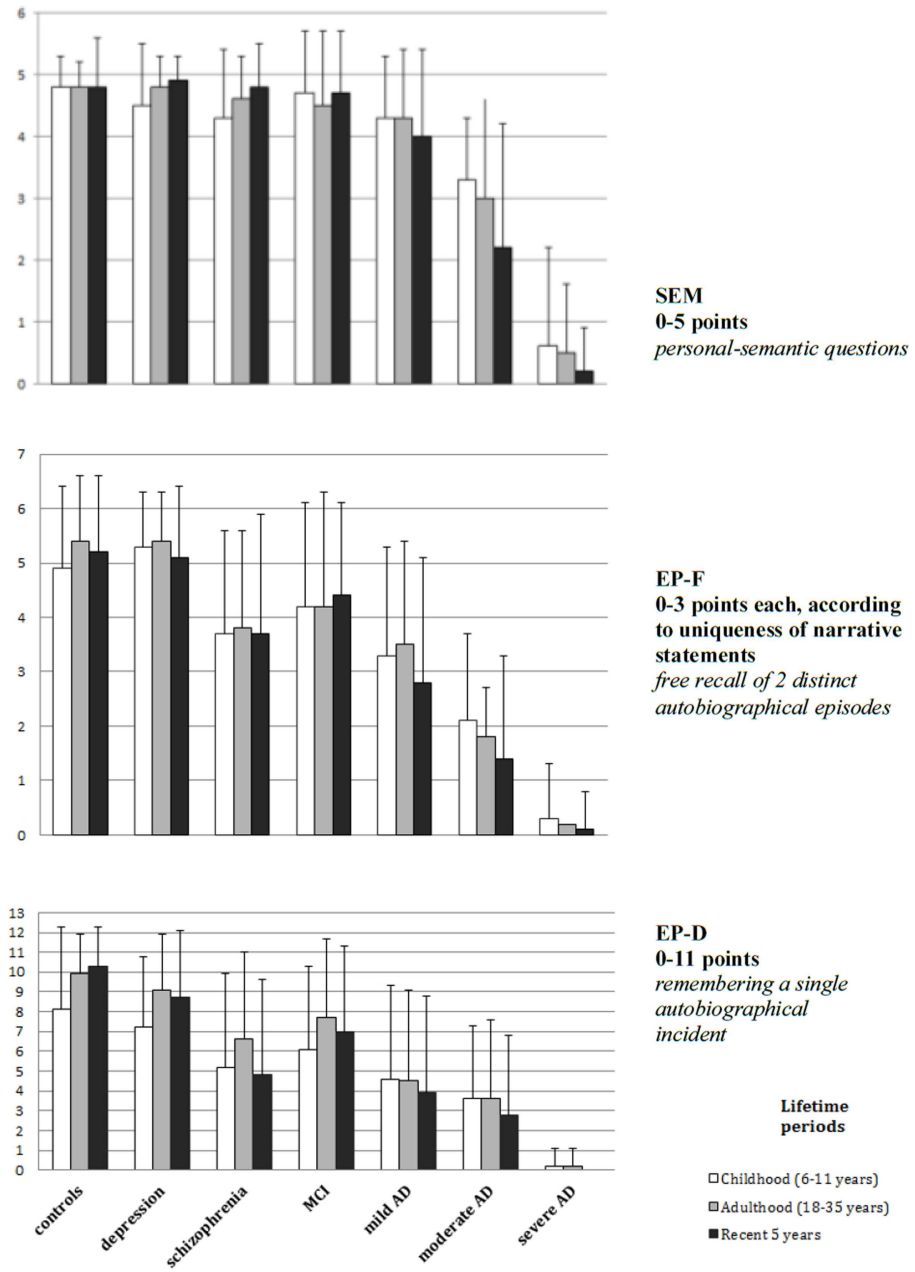


FIGURE 1 | Group comparison concerning semantic knowledge (SEM), free recalled episodes (EP-F) and episodic details (EP-D) by groups of patients with depression (Ahlsdorf, 2009), schizophrenia (Herold et al., 2013), MCI, different stages of AD and healthy controls (Seidl et al., 2011).

major depression and patients with MCI than in those with manifest AD. Similar results applied for the EP-D which were significantly higher in the healthy controls followed by patients with MCI and major depression than in those with manifest AD. Only marginally, non-significant differences in EP-D scores between healthy controls and patients with major depression could be found. The E-AGI total values diminished non-significantly in patients with major depression in comparison to healthy controls. The study yielded an important result in the comparison of the evaluation of memories. Patients with major depression were occupied with negative thoughts and estimated their memories more negative than patients with AD.

STUDY 2: ABM IN NURSING HOME RESIDENTS WITH MCI AND MANIFEST AD (SEIDL ET AL., 2011)

Autobiographical memory was examined in patients with different stages of AD and MCI, respectively, as well as in healthy controls (**Table 1**). Subjects were recruited in the framework of a large survey in nursing homes across Germany.

Results (**Figure 1**) demonstrated a progressive loss of ABM sum scores with increasing severity of dementia, which primarily involved episodic rather than semantic memories. When compared between controls, MCI, and mild AD diagnostic groups, SEM scores showed only minor, non-significant differences. Patients with moderate and severe AD displayed a significant reduction in SEM from the recent 5 years. Patients with moderate AD showed also a reduction for EP-F scores from the recent 5 years when compared to the childhood period whereas in healthy controls an inverse relationship was observed. This dissociation indicates that these memory functions are subserved by distinct neuronal systems as emphasized by the multiple trace hypothesis.

Further analyses of the temporal gradients in control subjects and MCI patients displayed a better memory performance from adulthood when compared to the childhood period. Both controls and patients with MCI showed lower EP-D scores for the childhood period.

In contrast, this recency effect was not found in patients with moderate AD suggesting an impact of the disease on the formation of recent memories.

STUDY 3: ABM IN NORMAL AGING AND MCI (BERNA ET AL., 2012)

Results confirmed a significant impairment of episodic ABM in MCI, but not in normal aging. Old-aged patients with MCI reached significantly lower scores than both Healthy Middle-Aged ($P < 0.001$) and Healthy Old-Aged ($P = 0.02$) subjects. Significant lower scores were also reached by Old-Aged patients with MCI compared with healthy Middle-Aged patients in the recent period ($P = 0.004$). Participants with MCI showed significantly lower scores than both control groups irrespective of age. These deficits were significantly correlated with verbal memory performances, but not with measures of executive functions.

STUDY 4: HIPPOCAMPAL CHANGES AND ABM IN MCI AND AD (THOMANN ET AL., 2012)

Autobiographical memory deficits were investigated with respect to hippocampal changes in patients with MCI ($n = 15$), patients with mild AD and cognitively unaffected control subjects ($n = 24$) (**Table 1**). Associations between ABM sum scores and hippocampal changes were explored using partial correlations, each of the significant correlations was confirmed by regional shape analyses. Results confirmed a significant ABM loss in the in early stages of AD and in MCI. Episodic, but not semantic ABM losses were associated with hippocampal atrophy mainly involving the left hippocampus. Right-sided hippocampal atrophy corresponded to reduced scores in the EP-F of the "childhood" lifetime period. These associations referred to the regional rather than to the global hippocampal changes which primarily affect the hippocampal head and body.

STUDY 5: ABM DEFICITS IN CHRONIC SCHIZOPHRENIA (HEROLD ET AL., 2013)

Autobiographical memory BM and hippocampal volume were assessed in 33 patients with chronic schizophrenia ($n = 24$) or patients with schizoaffective disorder ($n = 9$) and 21 healthy volunteers matched for age, gender, and education. The assessment of ABM was part of a large neuropsychological test battery, which also addressed verbal, short-term, and working memory as well as remote semantic memory. Psychopathological symptoms were rated on appropriate rating scales (**Table 1**).

When compared with the healthy controls, patients showed a significantly poorer recollection of episodic ABM as well as a trend toward a lower performance with respect to semantic ABM. Analysis of MRI data revealed lower volumes of left anterior and posterior hippocampus as well as of the right posterior hippocampus in the patients group.

Both, episodic and semantic ABM-scores were significantly correlated with the left hippocampal volume in the patient group. This association applied for both, the left anterior as well as the left posterior part of the hippocampus. These associations accounted for 16% of the variance of episodic ABM and 24% of the variance of semantic ABM with educational level considered as a covariate.

DISCUSSION

The present studies yielded the following main findings: (i) a confirmation that episodic rather than semantic ABM is impaired in major psychiatric conditions such as AD and chronic schizophrenia; (ii) evidence that this effect is not accounted for by potential confounding factors such as age, education, or depressed mood; and (iii) an indication that ABM deficits refer to hippocampal changes in both AD and chronic schizophrenia.

That episodic rather than semantic ABM is impaired already in the early stages of AD including MCI is made evident by a wealth of studies. This effect involves the recognition of past events and also includes the remembrance of recent experiences such as a consultation in the doctors' office and can facilitate clinical examination and diagnosis in early dementia (Donix et al., 2010). While semantic recall followed Ribot's law in patients with manifest dementia in all stages, episodic ABM recall showed this effect in patients with mild and moderate dementia only, since the respective deficits also included earlier life time periods.

A significant effect of potential confounding variables – in particular age, education, or depressed mood – on these findings was not confirmed. Age is a variable difficult to consider in any study on AD since the disease progresses with it. We therefore investigated

potential age effects in a 332 otherwise healthy volunteers from two birth cohorts and demonstrated only minor non-significant episodic ABM differences with age. School education had to be considered as another potential confounder since this variable is a robust marker of cognitive reserve (Fratiglioni and Wang, 2007; Sattler, 2011; Schröder and Pantel, 2011). However, an effect of school education could not be confirmed (Berna et al., 2012). Depressive mood was primarily considered by Ahlsdorf (2009) who described an effect on the emotional content of the memories reported rather than their recollection *per se*. Depressed patients showed a significantly higher rate of negative valuations in both, semantic and episodic ABM. Along with this, Seidl et al. (2011) did not find the severity of ABM deficits to be significantly correlated with depressive mood although their sample of 239 nursing home residents provided a sufficient effect size.

Two of the studies summarized here – each one involving patients with MCI and AD or patients with chronic schizophrenia – investigated ABM deficits with respect to MRI derived measures of hippocampal volume and shape. Irrespective of the diagnosis, episodic ABM deficits were associated with left hippocampal changes. An additional association of ABM deficits with right hippocampal changes was restricted to patients with MCI and AD. The respective associations clearly underline the importance of the hippocampus for the recollection of episodic ABM although these associations only accounted for a small proportion of the variance. Beginning in the early 1990s a wealth of neuroimaging studies found the hippocampus to be critically involved in MCI, AD, and chronic schizophrenia (Pantel et al., 1997; Heckers et al., 1998; Herold, 2011; Schröder and Pantel, 2011). Hence, it is plausible that the respective changes may result in similar deficits in both conditions. Differences refer to the extent of hippocampal changes and ABM deficits as well as to additional factors contributing to them. Further studies need to differentiate the association of hippocampal changes and ABM deficits by comparing hippocampal substructures for potential differences between these conditions or by considering additional clinical factors such as lifelong withdrawal, living without partnership, or long term hospitalization in patients with schizophrenia. Taken together, these finding conform with the multiple trace theory. Episodic ABM was already compromised in MCI and mild AD whereas recall of SEM was still preserved. This dissociation is generally referred to the hippocampus role for the recall of episodic but not semantic ABM since the former is already involved in the early and in the preclinical stages of AD (Pantel et al., 2003).

The results of our studies correspond to Conway's formal differentiation of event-specific knowledge and "general events" or "lifetime periods" (Conway, 1996; Conway and Pleydell-Pearce, 2000). From a more phenomenological standpoint, the failure of episodic remembrance in the more advanced stages of AD and schizophrenia causes a breakdown of subjective coherence and identity since life stories (McAdams, 1985) stop to be accessible nor retrievable anymore. This effect may be associated with psychopathological symptoms such as apathy which is another common features in both AD and chronic schizophrenia.

In conclusion the present studies underline the importance of episodic ABM changes in MCI, AD, and chronic schizophrenia, i.e., conditions which share hippocampal changes as a common feature. While deficits of episodic ABM are already present in the early stages of AD, those of semantic ABM are confined to the more severe stages. In both, AD and chronic schizophrenia, ABM deficits were correlated with hippocampal changes. These findings demonstrate that ABM deficits can facilitate the clinical examination of patients with MCI, AD, and chronic schizophrenia.

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REFERENCES

Ahlsdorf, E. (2009). *Differenzielle Untersuchungen zum Autobiographischen Gedächtnis. Ein Vergleich von gesunden älteren Menschen und Patienten mit leichter kognitiver Beeinträchtigung, beginnender Alzheimer Demenz sowie depressiver Episode.* Hamburg: Verlag Dr. Kovac; Band, 145.

Berna, F., Schönknecht, P., Seidl, U., Toro, P., and Schröder, J. (2012). Episodic autobiographical memory in normal aging and mild cognitive impairment: a population-based study. *Psychiatry Res.* 200, 807–812. doi:10.1016/j.psychres.2012.03.022

Conway, M. A. (1996). "Autobiographical knowledge and autobiographical memories," in *Remembering Our Past: Studies in Autobiographical Memory*, ed. D. C. Rubin (Dordrecht: Kluwer), 167–119.

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–228. doi:10.1037/0033-295X.107.2.261

Conway, M. A., Turk, D. J., Miller, S. L., Logan, J., Nebes, R. D., Meitzer, C. C., et al. (1999). A positron emission tomography (PET) study of autobiographical memory retrieval. *Memory* 7, 679–702. doi:10.1080/096582199387805

Cuervo-Lombard, C., Jovenin, N., Hedelin, G., Rizzo-Peter, L., Conway, M. A., and Danion, J. M. (2007). Autobiographical memory of adolescence and early adulthood events: an investigation in schizophrenia. *J. Int. Neuropsychol. Soc.* 13, 335–343. doi:10.1017/S135561770707035X

Dall'Ora, P., Della Salla, S., and Spinnler, H. (1989). Autobiographical memory. Its impairment in amnesic syndromes. *Cortex* 25, 197–217. doi:10.1016/S0010-9452(89)80037-1

Donix, M., Brons, C., Jurjanz, L., Poettrich, K., Winiecki, P., and Holthoff, V. A. (2010). Overgenerality of autobiographical memory in people with amnestic mild cognitive impairment and early Alzheimer's disease. *Arch. Clin. Neuropsychol.* 25, 22–27. doi:10.1093/arclin/acp098

Dorrego, M. F., Sabe, L., Garcia Cuerva, A., Kuzis, G., Tiberti, C., Boller, F., et al. (1999). Remote memory in Alzheimer's disease. *J. Neuropsychiatry Clin. Neurosci.* 11, 490–497.

Fast, K., Fujiwara, E., Schröder, J., and Markowitsch, H. J. (2007). *Erweitertes Autobiographisches Gedächtnisinterview (E-AGI)*. Frankfurt: Harcourt.

Fratiglioni, L., and Wang, H.-X. (2007). Brain reserve hypothesis in dementia. *J. Alzheimers Dis.* 12, 11–22.

Greene, J. D., and Hodges, J. R. (1996). Identification of famous faces and famous names in early Alzheimer's disease. Relationship to anterograde episodic and general semantic memory. *Brain* 119, 111–128. doi:10.1093/brain/119.1.111

Heckers, S., Rauch, S. L., Goff, D., Savage, C. R., Schacter, D. L., Fischmann, A. J., et al. (1998). Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat. Neurosci.* 1, 318–323. doi:10.1038/1137

Herold, C. J. (2011). "Zerebrale Korrelate des autobiographischen Gedächtnisses bei schizophrenen Psychosen," in *Chronische Schizophrenien*, eds J. Schröder and F. G. Brecht (Heidelberg: AKA GmbH), 85–105.

Herold, C. J., Lässer, M. M., Schmid, A. L., Seidl, U., Kong, L., Fellhauer, I., et al. (2013). Hippocampal volume reduction and autobiographical memory deficits in chronic schizophrenia. *Psychiatry Res Neuroimaging* 211, 189–194. doi:10.1016/j.pscychresns.2012.04.002

Hou, C. E., Miller, B. L., and Kramer, J. H. (2005). Patterns of autobiographical memory loss in dementia. *Int. J. Geriatr. Psychiatry* 20, 809–815. doi:10.1002/gps.1361

Kopelman, M. D. (1989). Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia* 27, 437–460. doi:10.1016/0028-3932(89)90050-X

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1990). *Autobiographical Memory Inventory*. Bury St Edmunds: Thames Valley Test Company.

Leyhe, T., Muller, S., Milian, M., Eschweiler, G. W., and Saur, R. (2009). Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia* 47, 2464–2469. doi:10.1016/j.neuropsychologia.2009.04.018

Markowitsch, H. J. (2003). "Memory: disturbances and therapy," in *Neurological Disorders Course and Treatment*, 2nd Edn, eds T. Brandt, L. Caplan, L. Dichgans, H. C. Diener, and C. Kennard (San Diego: Academic Press), 287–302.

McAdams, D. P. (1985). *Power, Intimacy and the Life Story*. Homewood, IL: Dorsey Press.

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* 7, 217–227. doi:10.1016/S0959-4388(97)80010-4

Noulhiane, M., Piolino, P., Hasboun, D., Clemenceaue, S., Baulac, M., and Samson, S. (2008). Autonoetic consciousness in autobiographical memories after medial temporal lobe resection. *Behav. Neurol.* 19, 19–22.

Pantel, J., Kratz, B., Essig, M., and Schröder, J. (2003). Parahippocampal volume deficits in subjects with aging-associated cognitive decline. *Am. J. Psychiatry* 160, 379–382. doi:10.1176/appi.ajp.160.2.379

Pantel, J., Schröder, J., Schad, L. R., Friedlinger, M., Knopp, M. V., Schmitt, R., et al. (1997). Quantitative magnetic resonance imaging and neuropsychological functions in dementia of the Alzheimer type. *Psychol. Med.* 27, 221–229. doi:10.1017/S003329179600431X

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De la Sayette, V., et al. (2003). Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. *Brain* 126, 2203–2219. doi:10.1093/brain/awg222

Piolino, P., Giffard-Quillon, G., Desgranges, B., Chetelat, G., Baron, J. C., and Eustache, F. (2004). Re-experiencing old memories via hippocampus: a PET study of autobiographical memory. *Neuroimage* 22, 1371–1383. doi:10.1016/j.neuroimage.2004.02.025

Ribot, T. (1881). *Les maladies de la mémoire*. Paris: Germer-Baillière.

Sagar, H. J., Cohen, N. J., Sullivan, E. V., Corkin, S., and Growdon, J. H. (1988). Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain* 111, 185–206. doi:10.1093/brain/111.1.185

Sattler, C. (2011). *Kognitive Reserve im Alter – Wechselwirkungen neuropsychologischer, sozialer und neurobiologischer Faktoren im Vorfeld demenzielle Erkrankungen*. Heidelberg: Karl-Ruprecht-Universität.

Schröder, J., and Pantel, J. (2011). *Die leichte kognitive Beeinträchtigung – Klinik, Diagnostik, Therapie und Prävention im Vorfeld der Alzheimer Demenz*. Stuttgart: Schattauer-Verlag.

Seidl, U., Lueken, U., Thomann, P. A., Geider, J., and Schröder, J. (2011). Autobiographical memory deficits in Alzheimer's disease. *J. Alzheimers Dis.* 27, 567–574. doi:10.3233/JAD-2011-110014

Squire, L., and Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177. doi:10.1016/0959-4388(95)80023-9

Steinvorth, S., Levine, B., and Corkin, S. (2005). Medial temporal lobe structures are needed to re-experience remote autobiographical memories: evidence from H.M. and W.R. *Neuropsychologia* 43, 479–496. doi:10.1016/j.neuropsychologia.2005.01.001

Thomann, P. A., Seidl, U., Brinkmann, J., Hirjak, D., Traeger, T., Wolf, R. C., et al. (2012). Hippocampal morphology and autobiographic memory in mild cognitive impairment and Alzheimer's disease. *Curr. Alzheimer Res.* 9, 000–000. doi:10.2174/156720512800492558

Tulving, E. (1972). "Episodic and semantic memory," in *Organization and Memory*, Vol. 1972, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–403.

Tulving, E. (1983). *Elements of Episodic Memory*. Oxford: Clarendon Press.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 125. doi:10.1146/annurev.psych.53.100901.135114

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204. doi:10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.3.CO;2-J

Viard, A., Piolino, P., Desgranges, B., Chetelat, G., Lebreton, K., Landeau, B., et al. (2007). Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: an fMRI study. *Cereb. Cortex* 17, 2453–2467. doi:10.1093/cercor/bhl153

Viskontas, I. V., McAndrews, M. P., and Moscovitch, M. (2000). Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. *J. Neurosci.* 20, 5853–5857.

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Impairments in episodic-autobiographical memory and emotional and social information processing in CADASIL during mid-adulthood

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) – is the most common genetic source of vascular dementia in adults, being caused by a mutation in NOTCH3 gene. Spontaneous *de novo* mutations may occur, but their frequency is largely unknown. Ischemic strokes and cognitive impairments are the most frequent manifestations, but seizures affect up to 10% of the patients. Herein, we describe a 47-year-old male scholar with a genetically confirmed diagnosis of CADASIL (Arg133Cys mutation in the NOTCH3 gene) and a seemingly negative family history of CADASIL illness, who was investigated with a comprehensive neuropsychological testing battery and neuroimaging methods. The patient demonstrated on one hand severe and accelerated deteriorations in multiple cognitive domains such as concentration, long-term memory (including the episodic-autobiographical memory domain), problem solving, cognitive flexibility and planning, affect recognition, discrimination and matching, and social cognition (theory of mind). Some of these impairments were even captured by abbreviated instruments for investigating suspicion of dementia. On the other hand the patient still possessed high crystallized (verbal) intelligence and a capacity to put forth a façade of well-preserved intellectual functioning. Although no definite conclusions can be drawn from a single case study, our findings point to the presence of additional cognitive changes in CADASIL in middle adulthood, in particular to impairments in the episodic-autobiographical memory domain and social information processing (e.g., social cognition). Whether these identified impairments are related to the patient's specific phenotype or to an ascertainment bias (e.g., a paucity of studies investigating these cognitive functions) requires elucidation by larger scale research.

Keywords: chromosome 19, gene mutation, episodic memory, problem solving, cognitive flexibility, social information processing

INTRODUCTION

In 1991, a French group (Tournier-Lasserve et al., 1991) described the occurrence of an "[a]utosomal dominant syndrome with strokelike episodes and leukoencephalopathy" (Title of the publication). They studied 45 family members and found in 9 of them transient ischemic attacks and strokes, together with widespread involvement of the white matter. Two years later they described autopsy findings of one of the nine patients – a woman who died at age 59 (Baudrimont et al., 1993). When this working group in 1993 coined the acronym cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) for this disease condition, they stated that related cases had been published since 1977 (Tournier-Lasserve et al., 1993). In a more recent review, Chabriat et al. (2009) remarked that the first case of CADASIL might have been described in 1955 in two sisters by van Bogaert (1955) and categorized at the time as Binswanger's disease.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is regarded as a hereditary, autosomal dominant "disease with high penetrance in which occlusion of small arteries in the brain of adults results in small deep brain infarcts and progressive accumulation of demyelination areas in the brain" (André, 2010, p. 287). Intrafamilial phenotypic variability has been reported. Phenotypic variations in monozygotic twins were identified and attributed to environmental factors and epigenetic effects (Dichgans et al., 1998; Mykkanen et al., 2004, 2009). *De novo* mutations and homozygous cases were also infrequently described (Chabriat et al., 2009). A mutation in the NOTCH3 gene in chromosome 19 apparently first leads to a microangiopathy of the small arteries supplying the brain, and – as a consequence – ultimately to dementia (Joutel et al., 1996). Magnetic resonance imaging (MRI) sometimes shows neural abnormalities from about age 30 onward, strokes may manifest themselves from about age 35 onward, mood disorders after age 40, and dementia may develop

between ages 50 and 60 (Sabbadini et al., 1995; Chabriat et al., 2009; André, 2010). Seizures may happen in 5–10% of the patients (Chabriat et al., 2009). Neuroimaging data typically include multifocal white matter lesions, which affect (anterior) temporal lobe and external capsula (Chabriat et al., 1995; Joutel et al., 1996; Brass et al., 2009; Jacqmin et al., 2010; Epelbaum et al., 2011). Changes in basal ganglia, thalamus, brainstem and corpus callosum, and frontal white matter can also be detected (Brass et al., 2009; Chabriat et al., 2009). There is no effective disease modifying treatment available (Dichgans et al., 2008).

Cognitive impairments are considered to be the second most common manifestation of CADASIL. Several studies have linked gene defects to changes in cognition; however, the relation between genotype and brain development and genotype and cognition is very complex. This might also hold true for aberrations related to chromosome 19 (Grimwood et al., 2004; Van der Aa et al., 2010). In patients with CADASIL, the development and progression of changes in cognition have prevailingly been connected to the occurrence of recurrent strokes, but other mechanisms may play a role (Amberla et al., 2004; Peters et al., 2005).

Executive dysfunctions, which were reported to already be present in patients with CADASIL of age 35–50 years, and alterations in processing speed belong to the initial cognitive changes (Peters et al., 2005; Chabriat et al., 2009). Other cognitive impairments, which have been described, are deficits in attention and concentration, visuo-spatial skills, language, verbal and visual memory, and reasoning (Chabriat et al., 2009). Performance on recognition tasks is usually relatively or partially preserved. According to our knowledge, there are no accounts of formal assessment of the retrograde episodic-autobiographical memory in patients with CADASIL with the autobiographical memory interview (Kopelman et al., 1990) or its variants. Most studies which were carried out in patients with CADASIL used testing paradigms, which corresponded to old views of episodic memory (e.g., testing of memory for lists of pairs of words) (Tulving, 1972). Some authors stated that autobiographical memory is "typically impaired from the early stages of Alzheimer's disease (AD) and vascular dementia" (Naylor and Clare, 2008, p. 591). Others argued that "in comparison with AD patients, those with a diagnosis of vascular dementia display a relative preservation of episodic memory" (Peters et al., 2005, p. 2078). One study reported impairments in facial affect recognition in patients with CADASIL (Valenti et al., 2013). Their sample of patients had a higher rate of co-morbid depressive symptoms, which may have confounded the findings. Furthermore, no other complex tests of face-emotion processing were carried out and no tests on social cognition were performed. Overall there is a dearth of data in the CADASIL population on the ability for social information processing (Adolphs, 2010), namely social *perception* (e.g., face perception), *social cognition* (theory of mind, empathy, social judgment), and *social regulation* (emotion regulation, monitoring/error correction, self-reflection, deception).

Herein, we aim to impart novel insights into the nature and extent of changes in the episodic-autobiographical memory and social information processing in CADASIL, by reviewing the neuropsychological profile of a patient with a diagnosis of CADASIL, possibly due to a *de novo* mutation in NOTCH3 gene, and a strong premorbid educational and occupational achievement, who became symptomatic in his early to mid forties.

CASE REPORT

SP is a 47-year old man who self referred to our facility for a neuropsychological assessment, several months after he had received a diagnosis of CADASIL. Apart from a long standing problem with color perception and a questionable history of meningoencephalitis in childhood, SP had reportedly been in good health until his early 40s, when he out of the blue experienced an episode of diplopia (double-seeing). SP sought medical advice. He received a diagnosis of cranial mononeuropathy with left trochlear nerve (IV) paresis of unclear etiology, and a brief treatment with glucocorticoids. The diplopia remitted after a couple of weeks. Serum and cerebrospinal fluid (CSF) laboratory results were negative. *Borrelia* serology was also interpreted as unremarkable at the time. X-rays of the thorax showed no abnormalities. A head computed tomography (CT) demonstrated no evidence of intracerebral bleeding, but pointed to modifications in prefrontal white matter. MRI provided no evidence of infarcts or tumors. It evidenced changes in the white matter, namely in the periventricular areas and corpus callosum. The brain changes were judged as being old at the time and attributed to a questionable history of meningoencephalitis in childhood. Two years later, SP experienced a recurrence of the diplopia, which was linked to unilateral abducens nerve (VI) palsy. While the etiology of the sixth nerve palsy could not be ascertained, the seemingly progressive white matter abnormalities detected by structural MRI raised at the time the suspicion of multiple sclerosis and prompted a comprehensive work up. The diplopia recovered after approximately 2 weeks after another brief trial of glucocorticoid anti-inflammatories. SP's symptoms however broadened. He developed word finding difficulties, dizziness, and problems with orientation. Later both complex focal seizures and grand mal seizures occurred. Thorough medical and laboratory investigations were carried out and several therapeutic trials were initiated. SP stopped driving an automobile and stated that he has not driven any since his diagnosis of seizures. Until CADASIL was proven by genetic studies, SP's working diagnoses encompassed multiple sclerosis, neuroborreliosis (Lyme's disease), viral encephalitis, a mitochondrial disease with leukoencephalopathy, a hereditary metabolic leukoencephalopathy, and a cerebral amyloid angiopathy. Serological screening testing with enzyme-linked immunosorbent assay (ELISA) was positive for IgG antibodies against *Borrelia burgdorferi* (markers of previous infection), but negative for IgM antibodies (markers of actual infection). Confirmatory Western immunoblot tests followed. They were negative for IgM antibodies against *B. burgdorferi*, but IgG blots yielded positive results. The CSF evaluations provided evidence of positive IgG antibodies against *B. burgdorferi*, but were again negative for IgM antibodies. CSF to serum anti-*B. burgdorferi* antibody index was however mildly elevated. CSF analysis was positive for oligoclonal IgG bands Type III, but revealed no proteinemia or pleocytosis or abnormalities in glucose and lactate levels. SP had no meningitis signs or symptoms. Serum cell blood counts and differentials, liver and renal function tests were within normal limits. Despite insufficient and debated evidence for active neuroborreliosis, SP received a 21-day parenteral course of a cephalosporin

antibiotic (Ceftriaxone 2 g a day), with unclear benefits. For the control of seizure activity, treatment with sodium divalproate was begun, with good seizure control and no significant subjective untoward effects. Contradictory findings of oligoclonal bands on the protein electrophoresis of CSF, a negative family history and progressive brain abnormalities affecting the white matter maintained for a substantial period the suspicion of multiple sclerosis (Zeman et al., 1993; Dichgans et al., 1999; Compston and Coles, 2008; Bentley et al., 2011). In the face of repeated and additional laboratory investigations the diagnosis of multiple sclerosis was subsequently discarded. Several factors strongly argued against viewing the infection with *B. burgdorferi* as a primary mechanism for the cognitive and physical changes of SP (Yamamoto et al., 2011; Eikeland et al., 2012), in addition to the genetic testing (see below). As mentioned above, SP received an adequate, evidence-based treatment with an antibiotic that is very active against Lyme borreliosis and crosses the blood–brain barrier (Stanek et al., 2012), despite questionable support for an active diagnosis of neuroborreliosis. There are indeed authors who argue that positive *B. burgdorferi* immunological markers in CSF may not mean that the individual has active neuroborreliosis (Roos and Berger, 2007). They reportedly could represent proof of a previous infection (Stanek et al., 2012) or leakage of antibodies from serum across the blood–brain barrier, in the context of a CADASIL-related increase in the permeability of the blood–brain barrier (Roos and Berger, 2007; Collongues et al., 2012). Furthermore, asymptomatic infection with *Borrelia* may occur relatively frequently in Europe (Steere et al., 2003). Additionally, the existence and magnitude of chronic courses of neuropsychological deficits after symptomatic *B. burgdorferi* infection are debated (Shadick et al., 1999; Eikeland et al., 2012; Stanek et al., 2012). Some authors reported that neuropsychological deficits pertaining to memory and executive functions may follow a chronic course (Eikeland et al., 2012) in a subset of patients, lasting for more than 6 months (post-Lyme borreliosis syndrome) (Stanek et al., 2012). Shadick et al. (1999) found that subjective memory impairments were reported by patients with a history of Lyme disease 6 years after the infection. However, performance on objective memory tests was deemed in this study as being comparable with that of matched healthy participants without a history of Lyme disease. Finally, although brain changes may occasionally persist after successful antibiotic treatment in neuroborreliosis (Agarwal and Sze, 2009; Hildenbrand et al., 2009), SP's pattern of brain changes had several unique elements that supported the final diagnosis of CADASIL (Chabriat et al., 2009) (see below). It was therefore concluded that the characteristics of the patient's features mandated consideration of other diagnostic entities.

Blood work results were remarkable for mildly increased homocysteine levels, slightly increased sodium levels, slightly increased hematocrit, low folic acid level, borderline low vitamin B_{12} levels, slightly increased glucosylated hemoglobin, and evidence of mild dyslipidemia. Cholesterol fractions HDL and LDL reached normal limits with lipid lowering medication (a statin). Serology for vasculitis and autoimmune diseases (systemic lupus erythematosus) and lues and human immuno deficiency virus (HIV) was negative. There was no indication of infection with cytomegalic virus, herpes simplex virus, *Toxoplasma gondii*, or active infection with varicella zoster. Thyroid function tests and ceruloplasmin plasma levels were within normal limits. Investigation of AD serum and CSF biomarkers yielded unremarkable results (Jahn, 2013). Due to suboptimal vitamin B values, replacement with both vitamin B_{12} and folic acid was instituted. An angiotensin converting enzyme inhibitor (ACEI) was apparently started for borderline blood pressure values, with good results. Electrocardiogram (ECG) studies revealed a normal sinus rhythm. Several electroencephalograms (EEG) were carried out. The most recent EEG with hyperventilation test was unremarkable. Electrophysiological investigations of tibial, peroneal, sural, and median nerves did not yield any significant results. Electromyography was unremarkable, with the exception of some unspecific changes of the right vastus lateralis muscle. The neuro-ophthalmology exam was suggestive of a sub-clinical optic nerve (II) neuropathy with bilateral pathological visual evoked potentials as well as bilateral temporal pallor of the papilla. Incidentally, optic nerve changes of ischemic origin in CADASIL were described in some case reports (Rufa et al., 2005) and delays in the visual cortical responses were also presented in case series (Parisi et al., 2000, 2003). Auditory evoked potentials were on the left side mildly slowed down, consistent with a change in the pontine area. Interestingly, abnormal brainstem auditory evoked potentials were also depicted in a member of one Italian family with CADASIL by Burganza et al. (1996). In the case of SP, the somato-sensory evoked potential of the median nerve was unremarkable.

Genetic testing was performed and confirmed an Arg133Cys mutation in the NOTCH3 gene, which has been linked to CADASIL in previous reports (Mykkanen et al., 2004, 2009). Given that both biological parents of SP were healthy and well above 71 years (the oldest age when CADASIL was ever reported to first manifest itself clinically) and that there was no clear evidence of a family history of CADASIL, a spontaneous *de novo* mutation was suspected (Joutel et al., 2000; Coto et al., 2006; Bentley et al., 2011; MacArthur et al., 2014). The results of genetic testing, neuroimaging, and the constellation of signs and symptoms supported the final diagnosis of CADASIL.

MATERIALS AND METHODS

NEUROIMAGING DATA EXAMINATION

Several imaging investigations were performed, such as CT scan of the brain (as described above), repeated head MRIs, ultrasound, and angiography. Extracranial and transcranial duplex ultrasound evidenced a normal vertebrobasilar artery and lack of significant changes in common carotid artery and external and internal carotid arteries. Magnetic resonance angiography of the head and neck yielded no significant abnormalities.

T1 and T2 sequences of his central nervous system were obtained with a conventional 1.5-T MRI device. Earlier scans pointed to abnormalities in periventricular white matter, corpus callosum, and centrum semiovale (Chabriat et al., 2009). Later, multiple lacunar lesions were described bilaterally in the basal ganglia and in the left frontal region. Abnormalities were also reported in the brainstem and signs of microbleeds were detected in the thalamus. The most recent neuroimaging exam (which was performed 1 month prior to the present neuropsychological examination) underlined the presence of chronic lacunar defects

and gliotic changes affecting bilaterally fronto-parietal regions and basal ganglia. Subacute lacunar infarcts were visualized in the left parietal white matter in addition. Lacunar defects at this time were also identified in the right temporal lobe and adjacent to the right amygdala. Gliotic changes affecting both anterior temporal lobes were also visualized. **Figure 1** illustrates the most relevant changes.

ANAMNESIS: PERSONAL AND FAMILY HISTORY

SP denied a history of alcohol or drug use. He reported several environmental allergies. The last neurological exam, performed several months before the assessment was significant for a left light facial paresis.

At the time of the neuropsychological assessment, SP was taking aspirin, a hypolipidemic drug (a statin), an ACEI drug for hypertension, a proton pump inhibitor medication for gastro-esophageal reflux, sodium divalproate for seizure protection, folic acid, and vitamin B_{12}. He reported tolerating well the medication and that both his seizures and blood pressure were well controlled on the current regimen. Last valproic acid trough blood levels were within therapeutic range.

SP's family history was significant for a sibling suffering from a hearing deficit with adult onset, of unclear origin (questionable acoustic neurinoma). Although cranial neuropathies including involvement of nerve VIII have occasionally been reported in patients with CADASIL, according to SP's knowledge his sibling's condition was stable and unremarkable for other symptoms. Parents were in their 70s and healthy according to SP's knowledge. SP described his birth and postpartum development as uneventful. According to his knowledge, he achieved developmental milestones at a normal age. SP reported being involved in a long-term romantic relationship. He was holding for several years an important and rewarding academic position in business and economy, but was faced with the prospects of a premature forced retirement since he had received the diagnosis of CADASIL. SP appeared still confident in his intellectual abilities and judged himself as being fit for his profession. Although SP had undergone other neuropsychological assessments in the past, he wanted to have a second opinion and therefore contacted our department for a new evaluation.

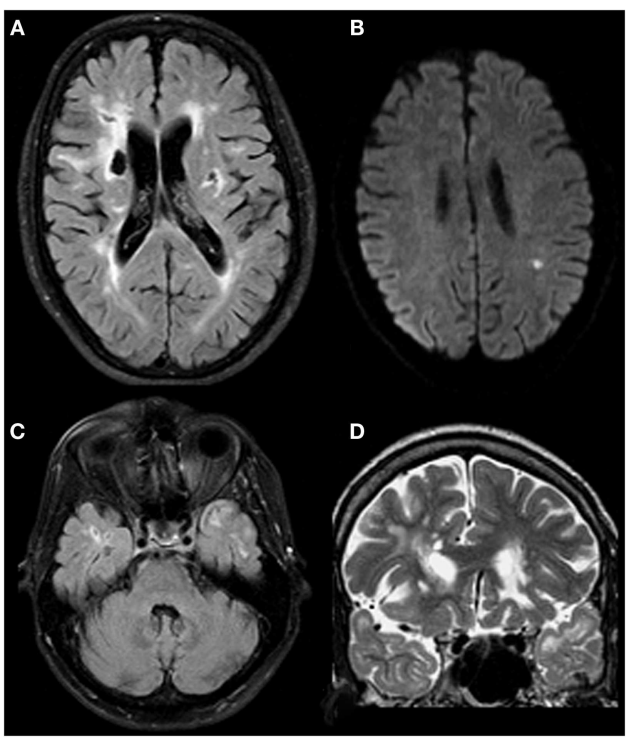


FIGURE 1 | Both chronic and acute changes in a patient with proven CADASIL. Chronic lacunar defects and gliotic changes affecting bilateral fronto-parietal regions including basal ganglia on both sides [**(A)**; axial FLAIR image]. Subacute lacunar infarct in the left parietal white matter [**(B)**; axial diffusion weighted image]. Gliotic changes affecting both anterior temporal lobes are thought to be typical for CADASIL [**(C,D)**; axial FLAIR and coronal T2 weighted images; please note: lacunar defects in the right temporal lobe are adjacent to the right-sided amygdala].

INFORMANT HISTORY

Informant history was obtained from SP's partner and from reviewing copies of consultants and health care provider reports, which SP made available to us. SP's partner did not elaborate on SP's difficulties, but opined that SP was still able to deal with the demands of his work, as they substantially relied on routines. SP alluded to some interpersonal difficulties with the partner that led to a temporary separation after his diagnosis with CADASIL, but did not give further details. In previous reports, it was remarked that SP had encountered difficulties at work since his diagnosis of CADASIL, where people had viewed him as scattered and questioned his professional competence. SP disagreed with these voiced concerns and stated that people questioned his work ability for strategic reasons. He perceived himself as being more patient than prior to his diagnosis. He denied problems with memory, although he admitted to engaging in computerized cognitive (including memory) training regularly. Health providers documented a reduction in affect range, mimic and gesturing, and voice monotony, but no conspicuous problems with personal boundaries. They noted that SP described having close social contacts with some co-workers, but no other regular social contacts.

NEUROPSYCHOLOGICAL EXAMINATION

For the purpose of the assessment, SP was interviewed and evaluated with several tests. SP gave informed written consent for the participation in the assessment and study and publication of the report. The study adhered to the declaration of Helsinki.

SP had a 1-day appointment in our unit, during which a substantial number of neuropsychological tests were administered. SP did not recall or report the nature of neuropsychological tests he had undergone in the past; however, the copies of health care providers reports indicated that he had at least one evaluation with consortium to establish a registry for AD (CERAD) test battery, more than 3 months prior to our meeting (Morris et al., 1988). This battery contains: mini-mental state examination (MMSE) (Folstein et al., 1977), the Trail Making Test part A and B, a test for phonetic fluency, an abbreviated version of the Boston naming test (15 items), a verbal fluency (animal category) test, a verbal memory test (word list), and a visual memory test and visuo-spatial skill tests.

The tests that were applied in our department were the following:

- Tests for handedness and brain lateralization: The lateral preference inventory (LPI) for measurement of handedness, footedness, earedness, and eyedness (Ehrenstein and Arnold-Schulz-Gahmen, 1997).
- Tests for the estimation of intelligence and overall cognitive status: Abbreviated Wechsler Adult Intelligence Test-Revised (Block test and Picture Completion test) (Dahl, 1972). MWWT-B or Mehrfachwahl-Wortschatz-Intelligenztest-B (Lehrl, 2005), a German version of the National Adult Reading Test NART (Nelson, 1982); DemTect, a dementia screening instrument consisting of six verbal and numerical subtests (Calabrese and Kessler, 2000); Mini-Mental-State-Examination (Folstein et al., 1977; Kessler et al., 1990).
- Tests for the evaluation of attention, concentration, and processing speed: Trail Making Test A and B (TMT-A + TMT-B; Lezak, 1995; Reitan, 1958); d2-Test (Brickenkamp and Zillmer, 1998); Attention Index of the German version of the Wechsler memory scale-revised (WMS-R; Härting et al., 2000).
- Tests for short-term memory and working memory: Wechsler memory scale-revised; digit span and block span forward and backward.
- Test for the evaluation of constructional functions and planning: Copy administration of the Rey–Osterrieth Figure Test (Osterrieth, 1944; Lezak, 1995).
- Tests for the evaluation of the verbal and non-verbal explicit anterograde long-term memory: Wechsler memory scale-revised (Härting et al., 2000); verbal learning memory test (VLMT) (Helmstaedter et al., 2001); Rey–Osterrieth-Figure (copy trial followed by delayed recall after 30 min) (Lezak, 1995); Doors Test of the Doors and People Test (Baddeley et al., 1994); Emotional Pictures Test (Cramon et al., 1993).
- Tests for the evaluation of retrograde memory: Extended autobiographical memory interview (Seidl et al., 2006), a German language adaptation of the autobiographical memory interview of Kopelman et al. (1990); Famous Faces Test (Fujiwara et al., 2008).
- Test for the evaluation of procedural memory: Mirror reading test (Cramon et al., 1993; Borsutzky et al., 2008, 2010). For the mirror reading test the variant that is presented by Borsutzky et al. (2008, 2010) was applied.
- Tests for the assessment of executive functions, including problem solving, cognitive flexibility: TMT-B (Lezak, 1995); Tower of Hanoi (Borys et al., 1982; Spitz et al., 1982; Lezak, 1995); California Card Sorting Test (Delis et al., 1992); problem solving test of Cronin-Golomb et al. (1987a,b); Wisconsin Card Sorting Test (Nelson, 1976).
- Tests of verbal fluency: Controlled Oral Word Association Test (COW; Golden et al., 2002); Supermarket task (word production; subtest of the DemTect); Boston naming test (Kaplan et al., 1983; Lezak, 1995; Spreen and Strauss, 1998; Golden et al., 2002).
- Tests for evaluation of malingering tendencies: Test of memory malingering (TOMM; Tombaugh, 1996; Teichner and Wagner, 2004; Greiffenstein et al., 2008); Rey 15-Item-Test (Lezak, 1995).
- Tests for evaluation of emotional processing: Florida Affect Battery (translated as Tübingen Affect Battery; Bowers et al., 1991; Breitenstein et al., 1996); Emotional Pictures Test (Cramon et al., 1993).
- Tests for mood, personality, and psychopathological and psychological load screening: Beck depression interview (BDI-II; Hautzinger et al., 2006); the symptom checklist revised or SCL-90R (Hessel et al., 2001); Freiburg-personality-inventory-revised (FPI-R; Fahrenberg et al., 2001). The SCL-90R assesses psychiatric symptom load and psychological distress. It contains nine subscales, such as somatization, obsessive–compulsiveness, interpersonal sensitivity, depression, anxiety, anger–hostility, phobic anxiety, paranoid thinking, and psychoticism. The general psychological distress level is appraised based on a global severity index, which is derived from all subscales. The FPI-R offers an assessment of personality across 12 dimensions: life satisfaction, social orientation, motivation to achieve, inhibition, excitability, aggressiveness, stress, physical complaints, health worries, openness, extraversion, and neuroticism. Furthermore, we gave SP a self-rating questionnaire in which he had to estimate how much his personality has changed from the time prior to the CADASIL diagnosis to the present (Crook and Larrabee, 1990; Fast and Fujiwara, 1999).
- Tests for social information processing (face-emotion perception, social cognition, risk-taking behavior): German adaptation of the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001; Reinhold and Markowitsch, 2007); Multiple-Choice-ToM-test (MCTT; Adenauer et al., 2005); Florida Affect Battery; Bowers et al., 1991); Game of Dice Test (Brand et al., 2005; Brand and Markowitsch, 2010). The Multiple-Choice-ToM-Test (Adenauer et al., 2005; Staniloiu et al., 2013) version that we used demanded the patient to read 16 short stories. (The test is available in two variants, one with 30 short written stories and another one with 16 stories.) After each story the patient had to infer the mental states of a protagonist of the story by making use of a forced multiple choice layout with four answering alternatives (but only one right answer). The multiple choice configuration allows distinguishing three different types of faults: (a) mental states inferences that are "excessive"; (b) mental states inferences that are "too positive"; (c) selection of the distractor answer that indicates a neutral answer (i.e., a non-mental state inference such as physical causation).

The game of dice task (Brand et al., 2005; Brand and Markowitsch, 2010) is a fictitious gambling setting, presented via computer, with explicit rules for virtual gains, losses, and winning stratagems. It evaluates decision-making under risk.

RESULTS

GENERAL BEHAVIORAL OBSERVATIONS

SP was cooperative, casually, but appropriately dressed, with good eye contact and fully oriented. He demonstrated willingness to take part in all tests and showed consistent effort to perform. He reported having some problems with concentration when too much interference was present. He subjectively appraised his memory as being good. He denied problems with mood, apart

from some anxiety feelings related to the future of his job. He voiced hope that the results of the tests would indicate that he still was fit to work in his profession. He answered readily all questions and worked without measurable or notable tendencies to worsen, distort or falsify his performance. He promptly followed instructions. SP was clinically unimpaired with respect to audition, but had, according to his report, a long standing history of a color perception deficit. The latter however did not appear to interfere in a conspicuous way with his ability to recognize colors on the applied tests or subtests that used colored items, such a subtest of WMS-R (Härting et al., 2000), the Doors Test of the Doors and People Test (Baddeley et al., 1994), or the Wisconsin Card Sorting Test.

Below we present and discuss the results of the tests that SP undertook over a period of about 7 h (with breaks). A summary of the findings of SP's evaluation is provided in **Table 1**.

LATERALITY

SP was clearly lateralized to the right.

LANGUAGE AND WORD KNOWLEDGE

SP's knowledge of terms and words, as assessed with the *Boston naming test*, was evidently above average (cf. **Table 1**). Given that a version of the *Boston naming test* had been administered several months prior to the assessment in our department, one might be inclined to attribute the results to a practicing effect. It is however noteworthy mentioning that the previously used variant only included 15 items. Furthermore, SP's performance at that time had been deemed within normal limits.

ATTENTION, CONCENTRATION, AND PROCESSING SPEED

SP's performance on tests of attention and concentration was non-uniform (cf. **Table 1**). In the Attention Index of the WMS-R he only gained 71 points. Similarly, in the *d2-test* his performance placed him in the lowest percentile. On the other hand, he achieved average scores in the *Trail Making Test A* and *B*. The results on *Trail Making Test A* and *B* were unexpected, given that a number of studies identified pronounced impairments in performance on these tests in patients with CADASIL without dementia and even without a history of stroke (Peters et al., 2005; Dichgans et al., 2008). Several factors might account for SP's execution of the last two tests. Possibly, the task required here was more similar to what SP did in his professional life compared to the tasks in the other two tests; therefore he had probably more routine and subsequently made less errors. Another clarification might be the practicing effect (Bartels et al., 2010). Although SP did not recall or communicate that he had these tests before, reviewing the copies of reports revealed that he had been tested with the *Trail Making Test A* and *B* several months prior and had at that time achieved below average scores. Furthermore, there are indications that SP engaged in self-directed training of cognitive abilities at home (Smith et al., 2007).

INTELLIGENCE AND GLOBAL COGNITIVE PERFORMANCE

Several evaluation procedures were used for assessing SP's intellectual abilities. The tests applied revealed that SP had a quite high verbal intelligence; however, his performance on both non-verbal parts of IQ testing and in tests that are used for preliminary investigation of the suspicion of dementia (*DemTect*, *MMSE*) was situated at low or borderline levels. As SP's academic formation and profession required verbal skills and a broad vocabulary to a considerable extent, the high scores on verbal intelligence tests are not surprising (Denzler et al., 1986; Christensen et al., 1997; Parkin and Java, 1999). They point to a stability of measures of crystallized intelligence (Christensen et al., 1997) on a background of high educational achievement in this patient, in comparison to measures of fluid intelligence (Christensen et al., 1997; Manard et al., 2014). The scores obtained with instruments for short assessment of suspicion of dementia were however surprisingly low, given SP's educational and occupational attainments. SP scored 27 on the *MMSE*. His performance on the *DemTect* [a global cognitive assessment instrument that includes measures for mental flexibility and verbal (category) fluency] was suggestive of "mild cognitive impairment" (cf. **Table 1**) (Peters et al., 2005). The discrepancy between the results on the two tests could be attributed to a larger degree of underestimation of executive dysfunction in *MMSE* (Benisty et al., 2008).

VISUAL-CONSTRUCTIVE SKILLS

Performance in copying the Rey–Osterrieth Figure was within normal limits (cf. **Table 1**). We did not find out evidence that he had taken part in this test before.

SHORT-TERM MEMORY AND WORKING MEMORY

In the Wechsler Memory Scale subtests for short-term and working memory he was somewhat impaired. In digit span forward he was normal, being able to repeat five digits. In all other measures (digit span backward, block span forward, and backward) he only achieved four digits.

LONG-TERM MEMORY

A large number of tests were applied to assess SP's long-term memory abilities. They can be grouped into tests of anterograde, retrograde, episodic-autobiographical, semantic, procedural, and priming memory (cf. Markowitsch and Staniloiu, 2012, and Tulving, 2005).

Anterograde memory

On all tests of anterograde memory – with the exception of two simple recognition tasks (*the less demanding section of the Doors test*, *Emotional Pictures Test*) – SP performed below the level of normal individuals. The finding of relatively preserved recognition in comparison to recall is congruent with other reports (Peters et al., 2005) (**Figure 2**). Verbal material was best retrieved (*VLMT*, *verbal memory index of the WMS-R*), while retrieval of visual material was the most compromised (*ROF*, *visual memory index of the WMS-R*, *complex part of the doors test*). Incidentally, these results are also consistent with other reports in the CADASIL literature (Amberla et al., 2004; Buffon et al., 2006). Interestingly, difficulties with retrieving visual material have also been reported in other conditions with lesions of fronto-striatal connections, such as Parkinson's disease (Smith et al., 2010; Souchay et al., 2013). Savage et al. (1999) proposed that fronto-striatal dysfunctions might lead to impairments in retrieving non-verbal material (Rey–Osterrieth Complex Figure) due to an organizational deficit in the copy condition, related to problems with shifting mental or spatial sets.

Table 1 | Summary of neuropsychological testing results.

Test/questionnaire	Score	Interpretation
LATERALITY		
Laterality preference inventory	15 right, 1 left	Right lateralized
QUESTIONNAIRES		
Self-evaluation prior to disease vs. present	SP only responds to parts of the questionnaire. He writes to be severely afraid of losing his job position, that his eating habits and hobbies have somewhat changed. He also noted changes in the relation with his partner, his ability to concentrate and act independently and that his interest in his disease has strongly increased	
Beck depression inventory	0	No tendency toward depression
Freiburg personality inventory	Stanines between 2 and 6	No serious conspicuousness
SCL-90-R	GSI: 0.38; PST: 24; PSDI: 1.375	Normal
ATTENTION AND CONCENTRATION		
Trail making test A + B	A: 43 s, 0 errors; B: 68 s, 0 errors	Average
d2-R test	75, 58 Omissions; PR < 1%	Massively deficient
WMS-R, attention and concentration	71	Massively deficient
INTELLIGENCE AND GENERAL INTELLECTUAL STATUS		
Mehrfach-Wahl-Wortschatz-test B (a test to estimate verbal IQ)	34 out of 37	High verbal IQ (130)
Abbreviated Wechsler intelligence test	Verbal: 22, 23; non-verbal: 12, 18	Verbal IQ above average, non-verbal subaverage
DemTect	10.5	"Mild cognitive impairment"
MMSE	27 Points	Borderline score which is, however, very low, given his intellectual background and age
VISUOCONSTRUCTIVE ABILITIES		
Rey–Osterrieth figure (ROF), copy	36 Points	Normal
SHORT-TEM AND WORKING MEMORY		
Digit span forward	5	Normal
Digit span backward	4	Subaverage
Block span forward	4	Impaired
Block span backward	4	Subaverage
ANTEROGRADE MEMORY		
ROF, reproduction after 1/2 h delay	4 Points	Severely impaired
WMS-R, general memory	78	Significantly below average
WMS-R, verbal memory	83	Significantly below average
WMS-R, visual memory	72	Significantly below average
WMS-R, long-term memory	56	Massively below average
VLMT	46 Learning, 6 interference, 11 and 6 in trials 6 + 7, and 42/7 in recognition	Below average
Doors test	A = 8 correct; B = 2 correct	Simple recognition (A) slightly below average, complex (B) severely below average
Emotional pictures test (recognition)	4 Errors	Normal

(Continued)

Table 1 | Continued

Test/questionnaire	Score	Interpretation
RETROGRADE MEMORY		
Famous faces test (38 pictures)	30 Directly recognized, 2 with cues	Above average
Autobiographical memory interview	Concrete remembrances reported, but few spontaneously	Subnormal
PROCEDURAL MEMORY		
Mirror reading task (two rounds)		Normal
LANGUAGE		
Boston naming test	All but 1 word identified	Above average
EMOTIONS RECOGNITION AND EMOTION INTERPRETATION		
Reading the mind in the eyes test	11/24 Correct	Below average
Multiple choice theory of mind test	8/16	Below average
FLORIDA AFFECT BATTERY		
Subtest 1 facial identity discrimination	11/20 Correct	Below average
Subtest 2 facial affect discrimination	14/20 Correct	Below average
Subtest 3 facial affect naming	13/20 Correct	Below average
Subtest 4 select facial affect	14/20 Correct	Below average
Subtest 5 facial affect matching	11/20 Correct	Below average
PROBLEM SOLVING, COGNITIVE FLEXIBILITY, EXECUTIVE FUNCTIONS, RISK TAKING		
Cronin-Golomb concept formation	16/17	Good average
Category test of Delis et al. (1992)	5, 4, and 3 categories	Below average
Tower of Hanoi (4 disks)	48 moves, 3 min, 1 s	Below average
Word fluency (controlled oral word test)	17 + 7 + 9	Below average (given his educational background)
Wisconsin card sorting test	27 Correct, 13 errors, 8 perseverative errors	Far below average
Game of dice task	With 18 moves −4400€ at end	No thoughtful strategy during first half of moves
TENDENCY TO MALINGER		
Rey 15-item test	All correct	No tendency of malingering
TOMM	First trial: 50/50	No tendency of malingering

One might argue that a more favorable performance on verbal memory tasks might reflect SP's background. Alternatively, it may bear connections with sub-clinical visual system impairments and partly with color perception abnormalities (Glen et al., 2012). SP's performance was particularly poor when a delay of half an hour had to be bridged between learning and free recall (*ROF*, *long-term memory index of the WMS-R*) (cf. **Table 1**).

Retrograde memory

Retrograde semantic memory recognition. SP recognized famous persons very well (*famous faces test*) (cf. **Table 1**).

Retrograde autobiographical memory recall. SP spontaneously generated an impoverished account of specific details of autobiographical episodes from this past (*autobiographical memory interview*), resembling in this respect patients with a prodrome of Alzheimer's dementia (Seidl et al., 2006). This finding might have been compounded in his case by the severe executive functions deficit (Brand and Markowitsch, 2008). Additionally, SP showed impaired retrieval of visual material. One might therefore argue that a compromised capacity to retrieve visual material might have also contributed to the production of schematic, overgeneralized autobiographical memories, with meager detail specificity (Bauer, 1982; Ogden, 1993; Greenberg et al., 2005; Smith et al., 2010; Souchay and Smith, 2013).

Procedural memory

SP's procedural skills, as assessed by his capacity to carry out *mirror image reading* appeared to be intact (cf. **Table 1**), despite presence of damage in the basal ganglia. Intact performance on the mirror

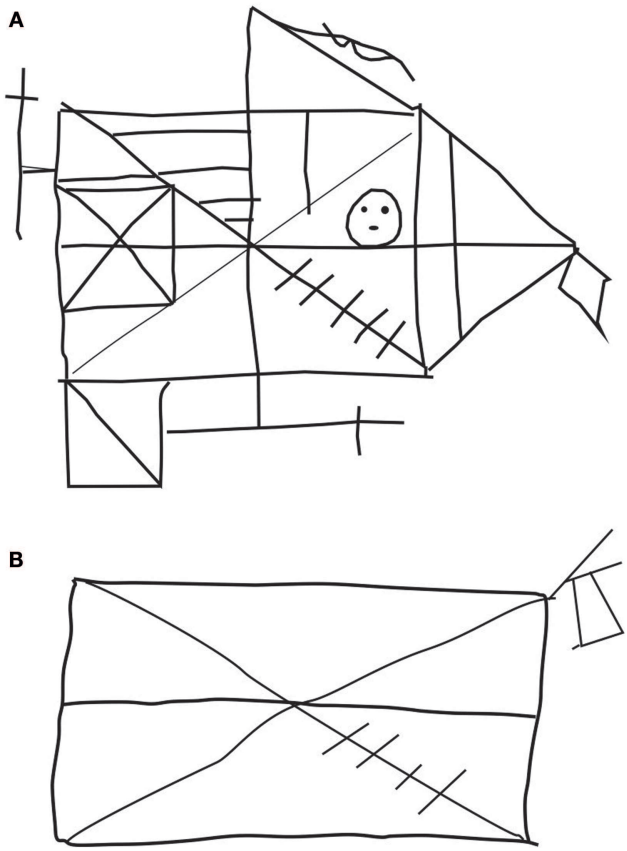


FIGURE 2 | Copying (A) and reproduction by heart after half an hour (B) of the Rey–Osterrieth figure.

image reading might reflect not only the preserved ability to learn and store new procedural skills, but may be supported by various cognitive components, including high levels of verbal intelligence (Markowitsch and Härting, 1996). Incidentally, other authors found uncompromised performance on mirror reading in patients with various fronto-striatal lesions (Schmidtke et al., 2002).

Malingering

In the two instruments applied to investigate tendencies for malingering (Rey 15-Item-Test; TOMM), SP performed without any error and subsequently showed no tendency to malinger (cf. **Table 1**). We did not expect SP to feign impairments, but administered these tests to be on the safe side with respect to interpreting his performance in tests of memory.

Executive functions, cognitive flexibility, risk taking, and problem solving abilities

SP's problem solving and executive abilities were largely impaired, with the only exceptions being the *TMT-B* and a test of *concept formation* (Cronin-Golomb et al., 1987a,b). We already commented above about the possible practicing effects on TMT-B test results, which may have led to improvements in performance over time. In the problem solving test of Cronin-Golomb et al. (1987a,b), SP was shown 17 sheets of paper; each leaf presented a drawing on the left side of the paper and three drawings on the right side (e.g., a crescent moon on the left side and a penguin, a woodpecker, and an owl on the right side). He had to tell which of the three drawings on the right side matches best the drawing on the left side. In this test, the correct answer can be given by simply excluding the more unlikely answers. In this way, the test resembles the more simple long-term memory tests, in which only recognition is required (as opposed to free recall).

In tests, where SP had to actively generate material or ideas – such as in the *California card sorting test* (Delis et al., 1992), the *tower of Hanoi*, the *word fluency* [*COW*], the *supermarket task*, and the *Wisconsin card sorting test* – his performance was impaired. In the *game of dice task*, SP behaved in strong contrast with his scholar background in business and economics. He showed no evidence of a sound or reasonable strategy about how to gain money in the fictitious game and consequently behaved randomly with respect to his choices. The findings of impairments in executive functions (planning, problem solving, set-shifting, cognitive flexibility, categorization, error detection, and monitoring) are in agreement with reports in the literature (Peters et al., 2005; Buffon et al., 2006). Contrary to other descriptions, we did not find evidence of relative preservation of performance on letter fluency tasks in comparison to category fluency tasks (Amberla et al., 2004; Dichgans, 2009).

Tests for social information processing (perception and interpretation of emotional states, theory of mind)

SP was impaired (partly even severely impaired) in tests of affect discrimination, naming, selection, and matching as well as facial identity discrimination [Florida (Tübingen) *Affect Battery* (*Subtests 1-*)]. *Tests for social cognition* ("Augen-ToM-Test" or *Reading the Mind in the Eyes Test* or RMET, *multiple choice theory of mind test or MCTT*) (cf. **Table 1**) yielded indices of below average performance as well. Both on Florida (Tübingen) Affect Battery subtests and "Augen-ToM-Test" SP encountered significant problems with the emotion of fear. Impairments in recognizing facial emotions (especially fear) have recently been reported in a group of patients with CADASIL by Valenti et al. (2013). In contrast to our patient, who showed no indication of depressive symptomatology, a substantial number of patients in the study of Valenti et al. (2013) endorsed depressive symptoms.

Tests for mood, personality, and psychopathological and psychological load screening

The screening instrument *Beck depression inventory* did not yield scores suggestive of an affective (depressive) disorder. The *symptom check list (SCL-90-R)* analysis did not generate abnormal scores. In the FPI-R, SP chose descriptors' values suggesting reduced life satisfaction, self-focused attitude, self control, very little aggressiveness, and moderately reduced concern about health. He perceived himself as being mildly introverted and emotionally stable. He experienced himself as being highly passive and with decreased motivation for achievement. The latter finding is of interest, given a high percentage of patients with CADASIL experiencing apathy (Chabriat et al., 2009). We however did not identify any conspicuous evidence of apathetic behavior. On the openness subscale of the *FPI-R*, SP scored within normal limits. In the *self-evaluation questionnaire*, SP only gave partial responses

with respect to changes since his CADASIL diagnosis. He indicated that he was very afraid of having to take a premature, forced retirement, and of losing his partner. He reported increased appetite and relinquishing some of his previous hobbies.

Figure 3 gives an overview of his test results, demonstrating that performance on a large array of the applied tests was on the deficient side. This is particularly evident in the illustration showing the distribution of inferior, normal, and superior test performance (**Figure 3B**), and especially for test results on anterograde memory, where his performance for all tests was situated on the inferior level (**Figure 3C**).

DISCUSSION

While the diagnosis of CADASIL is established (Hervé and Chabriat, 2010; Russell, 2010; Assareh et al., 2011; Yamamoto et al., 2011; Federico et al., 2012), case descriptions with a detailed neuropsychological examination identifying areas of deficiency and preservation can enrich the understanding of this condition and provide novel insights and ideas for larger scale research.

SP's case features a constellation of unique characteristics in our opinion. The clinical manifestations have included less common symptoms and findings, such as seizures, hypertension, diplopia, sub-clinical involvement of optic nerve as well as of the nerve VIII (André, 2010; Yamamoto et al., 2011). The misleading clinical presentation, pattern of laboratory results, and the seemingly negative family history of CADASIL are also atypical traits, which have posed a substantial challenge to securing a definitive diagnosis. The pattern of laboratory results pointed to features of dysregulated immunity. These features may have been underpinned by a history of infection with *B. burgdorferi* (Zeman et al., 1993). Alternatively, they may reflect an unusual form of CADASIL, with inflammatory-like processes (Dichgans et al., 1999; Bentley et al., 2011; Collongues et al., 2012). SP's distinctiveness might also pertain to his intellectual background and his profession. Another peculiar aspect is the progression of his cognitive functioning, encompassing marked deteriorations in a large number of cognitive domains being documented shortly after the diagnosis of CADASIL, limited insight into cognitive problems and reasonably maintained ability to put forth a façade of preserved intellectual functioning. SP did not endorse symptoms of depression and did not meet criteria for other psychiatric disorders. The bulk of neuropsychological examination results stayed in strong

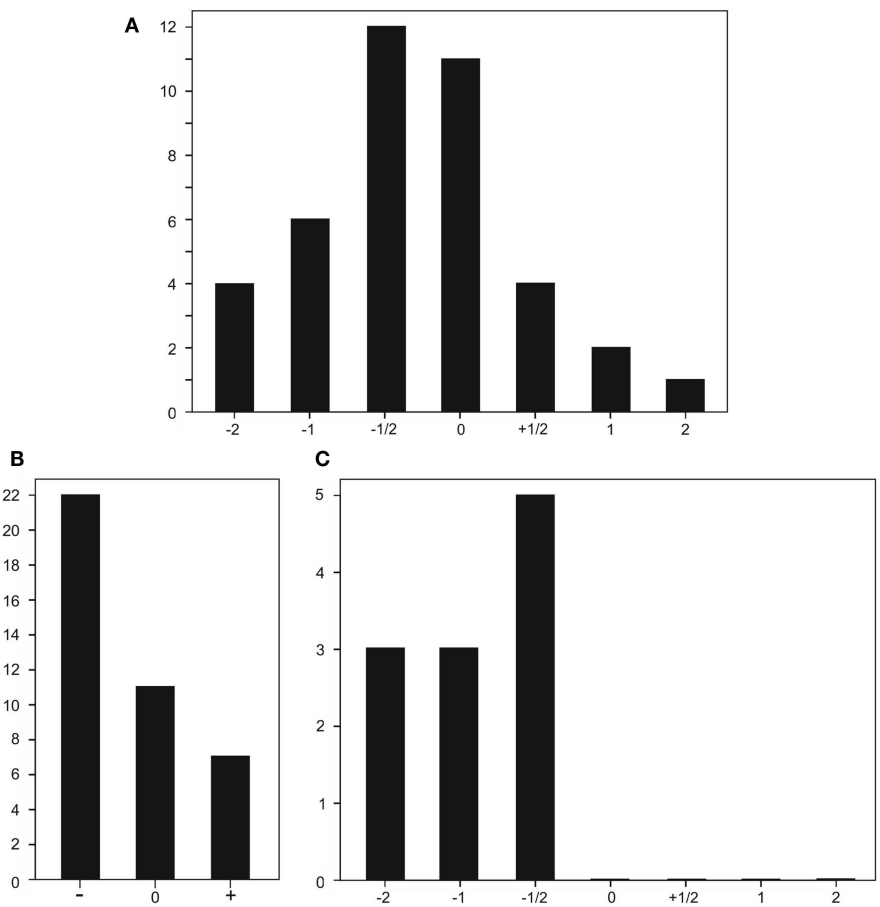


FIGURE 3 | Graphical illustrations of test results.
(A) Performance distribution in all 40 tests applied; scores roughly refer to standard deviations: 1/2 = less than a standard deviation below (−) or above (+) 0; ±1 or ±2 refer to about 1 or 2 standard deviations below or above baseline. **(B)** Performance distribution of tests with an inferior to normal (−), a normal (0), and a superior to normal performance (+). **(C)** Distribution of performance in tests measuring anterograde memory.

contradiction with his own appraisals of his cognitive difficulties. Furthermore, SP's structural imaging indicated substantial brain damage, involving subcortical structures, white matter as well as cortical areas.

Interestingly, SP's "crystallized" (verbally based) intelligence was still outstanding in one test and above average in another. This finding is in opposition to the results of Matsuda and Saito (1998) who in elderly patients with mild Alzheimer's dementia found deficits to be stronger in crystallized intelligence in comparison to age-matched healthy controls, while "fluid" intelligence measures did not deviate significantly from those of healthy participants. However, SP showed severely compromised performance on a number of intellectual measurements. In this way he resembled the three patients studied by Dominguez-Sanchez et al. (2011), who all lost a significant intelligence quotient and general intellectual capacity during the progression of CADASIL (7 years follow-up).

In the memory domain, SP showed a number of impairments. His subaverage performance in short-term memory and working memory tasks likely bears relations to changes in parietal and prefrontal areas (Markowitsch et al., 1999) and in frontal–subcortical circuits (Amberla et al., 2004). Massive impairments were noted on tests of anterograde (conscious) long-term memory. Similarly to his crystallized intelligence, his old knowledge was largely maintained. SP was still very able to recognize and name portraits of prominent persons (*famous faces test*). However, when he had to actively generate episodes of his own life, SP provided an impoverished, rudimentary, semanticized account.

SP's deficits with consciously acquiring mnemonic information for long-term storage could have stemmed from his damage to temporal as well as parietal areas and fiber connections (Markowitsch and Staniloiu, 2012; Staniloiu and Markowitsch, 2012). There are numerous meticulous documentations of anterograde memory impairments after bilateral damage of medio-temporal regions. Furthermore, studies show that hippocampal damage might be a route of impairment in anterograde conscious memory in CADASIL (as well as in patients with seizures) (Jokeit et al., 1997; O'Sullivan et al., 2009; Markowitsch and Staniloiu, 2012). Damage to the thalamus and diencephalic tracts may constitute another source of anterograde memory impairments in patients with CADASIL (Markowitsch, 1991; O'Sullivan et al., 2004; Chabriat et al., 2009; Markowitsch and Staniloiu, 2012). Interestingly, evidence of microbleeds in the thalamus was reported in the case of SP. Additionally, damage within prefrontal regions may also partly contribute to impairments in the acquisition of semantic and episodic mnemonic information for long-term storage (Rieger and Markowitsch, 1996; Markowitsch and Staniloiu, 2012).

As SP's ability for long-term concentration was impaired as well (particularly evident from the multiple omissions in the *d2-Test*), this might have added to both his anterograde and retrograde memory impairments. The attentional deficits may have stemmed from damage in parietal and frontal areas and their connections, and possibly from diencephalic and brainstem lesions (Mesulam, 1990). Parietal regions have been implicated not only in attentional processes, but also in short-term memory, episodic memory, self referential processing, and time perception (Babinsky et al., 1996; Beblo et al., 2001; Cabeza et al., 2011). They are opined to be engaged in modulation of top-down (frontal) and bottom-up (medial temporal lobe areas) episodic memory-related processes (Beblo et al., 2001; Cabeza et al., 2011; Souchay et al., 2013). The impairments in retrograde episodic-autobiographical memory observed in SP might deliver support for the idea that intact right fronto-temporal connections are important for "ecphorizing" old, emotionally tagged events (Fink et al., 1996; Kroll et al., 1997). As mentioned previously, SP had lacunar defects in the right temporal lobe and adjacent to the right amygdala as well as gliotic changes affecting both anterior temporal lobes.

Consistent with established descriptions in the literature, SP showed a pronounced executive dysfunction syndrome. Planning functions and the ability to overview necessary steps in solving more complex tasks were particularly deficient. This cannot only be inferred from SP's severe impairments in the *Wisconsin card sorting test* and *California card sorting test*, but also from the way he performed in the *d2-Test* where he should have crossed out all letters "d" which were accompanied by two small lines above or below them. He had a very high number of omissions, being apparently simply focused to reach the end of each of the 14 long letter lines – an aim usually impossible to accomplish.

A striking finding was the large extent of deficits in face-emotion processing tests and theory of mind tasks. In the Florida Affect Battery (Tübingen Affect Battery), SP's performance was compromised on both simple and complex tasks. These results might reflect damage of cortical and subcortical areas (and their fiber connections), which are recruited in face and emotion processing (Herholz et al., 2001; Vuilleumier et al., 2004; Markowitsch and Staniloiu, 2011). As mentioned above, in the case of SP we visualized lacunar defects in the right temporal lobe and in regions neighboring the right amygdala. Amygdalar dysfunction and/or damage of anterior hippocampus could lead to impairments of fear processing (Fanselow and Dong, 2010; Feinstein et al., 2011). The mentalizing deficits of SP might have originated from disruptions of temporal, parietal, and frontal regions and their connections (Abu-Akel, 2003) as well as damage of basal ganglia (Bodden et al., 2010; Kemp et al., 2013).

SP's apparently reduced insight and awareness into his cognitive deficits (especially in the memory domain) could have both biological and psychological underpinnings (Naylor and Clare, 2008; André, 2010). From a neuropsychological point of view, the diminished insight may mirror a collapsing executive system, faulty self knowledge updating processes, and impaired self awareness (Naylor and Clare, 2008; Klein and Gangi, 2010). With respect to neural correlates, these insight deficits may be underlain by the observed changes in fronto-parietal regions (Wagner et al., 2005; Stone et al., 2006; Metzinger, 2008; Nyberg et al., 2010; Souchay et al., 2013). From a psychological perspective, the deficient insight may reflect a desire to mask or deny his difficulties, in order to sustain a positive sense of identity (Naylor and Clare, 2008).

CONCLUSION

The present case report highlights a number of new as well as more established facets of CADASIL.

The most striking and novel aspect of our case is the extent of impairments in the episodic-autobiographical domain and social information processing (face-emotion processing, social cognition). These changes had not been documented to these

degrees in patients with CADASIL. Whether these identified impairments are related to the patient's specific phenotype (e.g., history of seizures, markers of dysregulated immunity) or to an ascertainment bias (e.g., a paucity of studies investigating these cognitive functions) will need to be clarified by larger scale research. The systematic investigation of social information processing in CADASIL patients is important as deficits in this domain might constitute hidden and often unrecognized and neglected sources of occupational and interpersonal difficulties. Although the informant history did not provide a clear corroboration of SP's deficits in social information processing, it is possible that at least some of his occupational and interpersonal difficulties might have been underpinned by his problems with social information processing.

Our case furthermore underlines the large phenotypic variability of CADASIL, which may be shaped by gene-environment interplays (Yamamoto et al., 2011). Although rarely reported, presentations with markers of dysregulated immunity might occur, as our case points to. The dysregulated immunity might reflect the presence of a concurrent infectious or immune condition, or a gene-environmental interplay (Bentley et al., 2011). These aspects have possible implications for the differential diagnosis and for the exploration of immune-modulating treatment approaches.

Finally, our case description suggests that the cognitive decline caused by CADASIL may follow a differentiated trajectory in patients with high intellectual and educational attainment in comparison to those with lower levels of educational and occupational achievement. In this respect CADASIL may have a similar impact on cognition as AD – though usually starting much earlier in life. For AD it has been repeatedly found that individuals starting from a high intellectual background will deteriorate faster and more profoundly than those starting from a moderate intellectual background (Scarmeas et al., 2006; Wilson et al., 2010). A high degree of cognitive reserve in patients with CADASIL might initially act as a buffer against the consequences of brain changes, braking the cognitive decline. When a critical burden of brain lesions is reached, this adaptation mechanism might break down, unraveling the consequences of brain damage and apparently getting translated into a more rapid cognitive decline in these patients in comparison to patients with a lower cognitive reserve (Perneczky et al., 2009). Though no firm conclusions can be drawn from studying a single case, our case report joins proposals for extending and making use of the concept of cognitive reserve for the understanding of vascular cognitive deficits (Stern, 2002; Zieren et al., 2013).

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REFERENCES

Abu-Akel, A. (2003). A neurobiological mapping of theory of mind. *Brain Res. Rev.* 43, 29–40. doi:10.1016/S0165-0173(03)00190-5

Adenauer, H., Kessler, J., Brand, M., Fleck, S., Lechmann, C., Prim, W., et al. (2005). "Vergleich verschiedener deutschsprachiger Theory-of-Mind Tests bei Menschen mit Asperger Syndrom [comparison of different German-language theory-of-mind tests in human beings with Asperger's syndrome]," in *Presentation at the 78 Congress of the German Society for Neurology* (Wiesbaden).

Adolphs, R. (2010). Conceptual challenges and directions for social neuroscience. *Neuron* 65, 752–767. doi:10.1016/j.neuron.2010.03.006

Agarwal, R., and Sze, G. (2009). Neuro-Lyme disease: MR imaging findings. *Radiology* 253, 167–173. doi:10.1148/radiol.2531081103

Amberla, K., Waljas, M., Tuominen, S., Almkvist, O., Poyhonen, M., Tuisku, S., et al. (2004). Insidious cognitive decline in CADASIL. *Stroke* 35, 1598–1602. doi:10.1161/01.STR.0000129787.92085.0a

André, C. (2010). Pathogenesis, clinical and radiological findings and treatment. *Arg. Neuropsiquiatr.* 68, 287–299. doi:10.1590/S0004-282X2010000200026

Assareh, A., Mather, K. A., Schofield, P. R., Kwok, J. B. J., and Sachdev, P. S. (2011). The genetics of white matter lesions. *CNS Neurosci. Ther.* 17, 525–540. doi:10.1111/j.1755-5949.2010.00181.x

Babinsky, R., Spiske, K., Engel, H., and Markowitsch, H. J. (1996). Attentional dysfunction associated with a discrete left parietal lesion. *Neurol. Psychiatr. Brain Res.* 4, 139–142.

Baddeley, A., Emslie, H., and Nimmo-Smith, I. (1994). *Doors and People Test.* Bury St. Edmunds: Thames Valley Test Company.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., and Plumb, I. (2001). The "reading the mind in the eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J. Child Psychol. Psychiatry* 42, 241–251. doi:10.1111/1469-7610.00715

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., and Ehrenreich, H. (2010). Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC Neurosci.* 11:118. doi:10.1186/1471-2202-11-118

Baudrimont, M., Dubas, F., Joutel, A., Tournier-Lasserve, E., and Bousser, M. G. (1993). Autosomal dominat leukoencephalopathy and subcortical ischemic stroke. A clinical study. *Stroke* 24, 122–125. doi:10.1161/01.STR.24.1.122

Bauer, R. M. (1982). Visual hypoemotionality as a symptom of visual-limbic disconnection in man. *Arch. Neurol.* 39, 702–708. doi:10.1001/archneur.1982.00510230028009

Beblo, T., Piefke, M., Driessen, M., Markowitsch, H. J., and Woermann, F. G. (2001). Contribution of retrosplenial and parietal brain regions to episodic memory: an fMRI study. *Neuroimage* 13(Part 2), S640. doi:10.1016/S1053-8119(01)91983-4

Benisty, S., Hernandez, K., Viswanathan, A., Reyes, S., Kurtz, A., O'Sullivan, M., et al. (2008). Diagnostic criteria of vascular dementia in CADASIL. *Stroke* 39, 838–844. doi:10.1161/STROKEAHA.107.490672

Bentley, P., Wang, T., Malik, O., Nicholas, R., Ban, M., Sawcer, S., et al. (2011). CADASIL with cord involvement associated with a novel and atypical NOTCH3 mutation. *J. Neurol. Neurosurg. Psychiatr.* 82, 855–860. doi:10.1136/jnnp.2010.223297

Bodden, M. E., Mollenhauer, B., Trenkwalder, C., Cabanel, N., Eggert, K. M., Unger, M. M., et al. (2010). Affective and cognitive theory of mind in patients with Parkinson's disease. *Parkinsonism Relat. Dis.* 16, 466–470. doi:10.1016/j.parkreldis.2010.04.014

Borsutzky, S., Fujiwara, E., Brand, M., and Markowitsch, H. J. (2008). Confabulations in alcoholic Korsakoff patients. *Neuropsychologia* 46, 3133–3143. doi:10.1016/j.neuropsychologia.2008.07.005

Borsutzky, S., Fujiwara, E., Brand, M., and Markowitsch, H. J. (2010). Susceptibility to false memories in patients with ACoA aneurysm. *Neuropsychologia* 48, 2811–2823. doi:10.1016/j.neuropsychologia.2010.05.023

Borys, S. V., Spitz, H. H., and Doans, B. A. (1982). Tower of Hanoi performance of retarded young adults and nonretarded children as a function of solution length and goal state. *J. Exp. Child Psychol.* 33, 87–110. doi:10.1016/0022-0965(82)90008-X

Bowers, D., Blonder, L. X., and Heilman, K. M. (1991). *The Florida Affect Battery.* Miami, FL: Florida University Press.

Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J., and Markowitsch, H. J. (2005). Decision-making deficits of Korsakoff patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology* 19, 267–277. doi:10.1037/0894-4105.19.3.267

Brand, M., and Markowitsch, H. J. (2008). "The role of the prefrontal cortex in episodic memory," in *Handbook of Behavioral Neuroscience: Episodic Memory Research*, Vol. 18, eds E. Dere, A. Easton, and J. P. Huston (Amsterdam: Elsevier), 317–342.

Brand, M., and Markowitsch, H. J. (2010). Mechanisms contributing to decision-making difficulties in late adulthood: theoretical approaches, speculations and empirical evidence. *Gerontology* 56, 435–440. doi:10.1159/000300569

Brass, S. D., Smith, E. E., Arboleda-Velasquez, J. F., Copen, W. A., and Frosch, M. P. (2009). Case records of the Massachusetts General Hospital. Case 12-2009. A 46-year-old man with migraine, aphasia, and hemiparesis and similarly affected family members. *N. Engl. J. Med.* 360, 1656–1665. doi:10.1056/NEJMcpc0810839

Breitenstein, C., Daum, I., Ackermann, H., Lütgehetmann, R., and Müller, E. (1996). Erfassung der Emotionswahrnehmung bei zentralnervösen Läsionen und Erkrankungen: psychometrische Gütekriterien der "Tübinger Affekt Batterie". *Neurol. Rehabil.* 2, 93–101.

Brickenkamp, R., and Zillmer, E. (1998). *The d2 Test of Attention*. Seattle, WA: Hogrefe & Huber.

Buffon, F., Porcher, R., Hernandez, K., Kurtz, A., Pointeau, S., Vahedi, K., et al. (2006). Cognitive profile in CADASIL. *J. Neurol. Neurosurg. Psychiatr.* 77, 175–180. doi:10.1136/jnnp.2005.068726

Burganza, M., Bertolasi, L., de Grandis, D., Bongiovanni, L. G., Polo, A., Cavallaro, T., et al. (1996). CADASIL: neurophysiological study of a large Italian family. *Electroencephalogr. Clin. Neurophysiol.* 98, 61. doi:10.1016/0013-4694(96)83500-0

Cabeza, R., Mazuz, Y. S., Stokes, J., Kragel, J. E., Woldorff, M. G., Ciaramelli, E., et al. (2011). Overlapping parietal activity in memory and perception: evidence for the attention to memory model. *J. Cogn. Neurosci.* 23, 3209–3217. doi:10.1162/jocn_a_00065

Calabrese, P., and Kessler, J. (2000). *DemTect*. Frankfurt: EISAI and Karlsruhe, Pfizer.

Chabriat, H., Joutel, A., Dichgans, M., Tournier-Lasserve, E., and Bousser, M. G. (2009). Cadasil. *Lancet Neurol.* 8, 643–653. doi:10.1016/S1474-4422(09)70127-9

Chabriat, H., Vahedi, K., Iba-Zizen, M. T., Joutel, A., Nibbio, A., Nagy, T. G., et al. (1995). Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet* 346, 934–939. doi:10.1016/S0140-6736(95)91557-5

Christensen, H., Korten, A. E., Jorm, A. F., Henderson, A. S., Jacomb, P. A., Rodgers, B., et al. (1997). Education and decline in cognitive performance: compensatory but not protective. *Int. J. Geriatr. Psychiatry* 12, 323–330. doi:10.1002/(SICI)1099-1166(199703)12:3<323::AID-GPS492>3.0.CO;2-N

Collongues, N., Derache, N., Blanc, F., Labauge, P., de Seze, J., and Defer, G. (2012). Inflammatory-like presentation of CADASIL: a diagnostic challenge. *BMC Neurol.* 12, 78. doi:10.1186/1471-2377-12-78

Compston, A., and Coles, A. (2008). Multiple sclerosis. *Lancet* 372, 1502–1517. doi:10.1016/S0140-6736(08)61620-7

Coto, E., Menendez, M., Navarro, R., Garcia-Castro, M., and Alvarez, V. (2006). A new de novo NOTCH3 mutation causing CADASIL. *Eur. J. Neurol.* 13, 628–631. doi:10.1111/j.1468-1331.2006.01337.x

Cramon, D. Y., von Markowitsch, H. J., and Schuri, U. (1993). The possible contribution of the septal region to memory. *Neuropsychologia* 31, 1159–1180. doi:10.1016/0028-3932(93)90065-8

Cronin-Golomb, A., Rho, W. A., Corkin, S., and Growdon, J. H. (1987a). Abstract reasoning in age-related neurological disease. *J. Neural Transm. Suppl.* 24, 79–83.

Cronin-Golomb, A., Rho, W. A., Corkin, S., and Growdon, J. H. (1987b). Relational abilities in Alzheimer's disease and Parkinson's disease. *Clin. Neuropsychol.* 1, 298.

Crook, T. H., and Larrabee, G. J. (1990). A self-rating scale for evaluating memory in everyday life. *Psychol. Aging* 5, 48–57. doi:10.1037/0882-7974.5.1.48

Dahl, G. (1972). *WIP-Reduzierter Wechsler-Intelligenztest [Abbreviated Wechsler Intelligence Test]*. Meisenheim am Glan: Hain.

Delis, D. C., Squire, L. R., Bihrle, A., and Massman, P. (1992). Componential analysis of problem-solving ability: performance of patients with frontal lobe damage and amnesic patients on a new card sorting test. *Neuropsychologia* 30, 683–697. doi:10.1016/0028-3932(92)90039-O

Denzler, P., Kessler, J., and Markowitsch, H. J. (1986). Possibilities and weaknesses of psychopathometric diagnosis of dementia. *Fortschr. Neurol. Psychiatr.* 54, 382–392. doi:10.1055/s-2007-1001943

Dichgans, M. (2009). Cognition in CADASIL. *Stroke* 40(Suppl.), S45–S47. doi:10.1161/STROKEAHA.108.534412

Dichgans, M., Markus, H. S., Salloway, S., Verkkoniemi, A., Moline, M., Wang, Q., et al. (2008). Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol.* 7, 310–318. doi:10.1016/S1474-4422(08)70046-2

Dichgans, M., Mayer, M., Uttner, I., Bruning, R., Muller-Hocker, J., Rungger, G., et al. (1998). The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann. Neurol.* 44, 731–739. doi:10.1002/ana.410440506

Dichgans, M., Wick, M., and Gasser, T. (1999). Cerebrospinal fluid findings in CADASIL. *Neurology* 53, 233. doi:10.1212/WNL.53.1.233

Dominguez-Sanchez, F. J., Lasa-Aristu, A., and Goni-Imizcoz, M. (2011). Intelligence impairment, personality features and psychopathology disturbances in a family affected with CADASIL. *Span. J. Psychol.* 14, 936–943. doi:10.5209/rev_SJOP.2011.v14.n2.39

Ehrenstein, W. H., and Arnold-Schulz-Gahmen, B. E. (1997). *Auge, Ohr, Hand und Fuß: Bestimmung des Individuellen Lateralitätsprofils [Eye, Ear, Hand and Foot: Determination of the Individual Laterality Profile]*. Dortmund: IfADo.

Eikeland, R., Ljostad, U., Mygland, A., Herlofson, K., and Lohaugen, G. C. (2012). European neuroborreliosis: neuropsychological findings 30 months post-treatment. *Eur. J. Neurol.* 19, 480–487. doi:10.1111/j.1468-1331.2011.03563.x

Epelbaum, S., Benisty, S., Reyes, S., O'Sullivan, M., Jouvent, E., During, M., et al. (2011). Verbal memory impairment in subcortical ischemic vascular disease: a descriptive analysis in CADASIL. *Neurobiol. Aging* 32, 2172–2182. doi:10.1016/j.neurobiolaging.2009.12.018

Fahrenberg, J., Hampel, R., and Selg, H. (2001). *Das Freiburger Persönlichkeitsinventar (FPI-R) [Freiburg Personality Inventory (FPI.R)]*, 7 Edn. Göttingen: Hogrefe.

Fanselow, M. S., and Dong, H. W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 65, 7–19. doi:10.1016/j.neuron.2009.11.031

Fast, K., and Fujiwara, E. (1999). *Selbsteinschätzungsfragebogen [Self-Rating Questionnaire]*. Bielefeld: University of Bielefeld.

Federico, A., Donato, I. D., Bianchi, S., Di Palma, C., Taglia, I., and Dotti, M. T. (2012). Hereditary cerebral small vessel disease: a review. *J. Neurol. Sci.* 322, 25–30. doi:10.1016/j.jns.2012.07.041

Feinstein, J. S., Adolphs, R., Damasio, A., and Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Curr. Biol.* 21, 34–38. doi:10.1016/j.cub.2010.11.042

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., and Heiss, W.-D. (1996). Cerebral representation of one's own past: neural networks involved in autobiographical memory. *J. Neurosci.* 16, 4275–4282.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1977). Minimal mental state: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi:10.1016/0022-3956(75)90026-6

Fujiwara, E., Brand, M., Kracht, L., Kessler, J., Diebel, A., Netz, J., et al. (2008). Functional retrograde amnesia: a multiple case study. *Cortex* 44, 29–45. doi:10.1016/j.cortex.2005.09.001

Glen, F. C., Crabb, D. P., Smith, N. D., Burton, R., and Garway-Heath, D. F. (2012). Do patients with glaucoma have difficulty recognizing faces? *Invest. Ophthalmol. Vis. Sci.* 53, 3629–3637. doi:10.1167/iovs.11-8538

Golden, C. J., Espe-Pfeifer, P., and Wachsler-Felder, J. (2002). *Neuropsychological Interpretation of Objective Psychological Tests*. New York, NY: Kluver.

Greenberg, D. L., Eacott, M. J., Brechin, D., and Rubin, D. C. (2005). Visual memory loss and autobiographical amnesia: a case study. *Neuropsychologia* 43, 1493–1502. doi:10.1016/j.neuropsychologia.2004.12.009

Greiffenstein, M. F., Greve, K. W., Bianchini, K. J., and Baker, W. J. (2008). Test of memory malingering and word memory test: a new comparison of failure concordance rates. *Arch. Clin. Neuropsychol.* 23, 801–807. doi:10.1016/j.acn.2008.07.005

Grimwood, J., Gordon, L. A., Olsen, A., Terry, A., Schmutz, J., Lamerdin, J., et al. (2004). The DNA sequence and biology of human chromosome 19. *Nature* 428, 529–535. doi:10.1038/nature02399

Härting, C., Markowitsch, H. J., Neufeld, H., Calabrese, P., Deisinger, K., and Kessler, J. (2000). *Die Wechsler-Memory-Scale Revised [Wechsler Memory Scale-Revised]*. Bern: Huber.

Hautzinger, M., Keller, F., and Kühner, C. (2006). *Beck-Depressionsinventar II (BDI-II) [Beck Depression Inventory]*. Frankfurt/Main: Harcourt Test Services.

Helmstaedter, C., Lendt, M., and Lux, S. (2001). *Verbaler Lern- und Merkfähigkeitstest (VLMT) [Verbal Learning and Memory Test]*. Göttingen: Hogrefe.

Herholz, K., Kessler, J., Ehlen, P., Lenz, O., Kalbe, E., and Markowitsch, H. J. (2001). The role of prefrontal cortex, precuneus, and cerebellum during face-name association learning. *Neuropsychologia* 39, 643–650. doi:10.1016/S0028-3932(00)00144-5

Hervé, D., and Chabriat, H. (2010). Cadasil. *J. Geriatr. Psychiatry Neurol.* 23, 269–276. doi:10.1177/0891988710383570

Hessel, A., Schumacher, J., Geyer, M., and Brähler, E. (2001). Symptom-checkliste SCL-90-R: testtheoretische überprüfung und normierung an einer bevölkerungsrepräsentativen stichprobe [symptom-check list SCL-90-R: test theoretical screening and standardization using a population representative sample]. *Diagnostica* 47, 27–39. doi:10.1026//0012-1924.47.1.27

Hildenbrand, P., Craven, D. E., Jones, R., and Nemeskal, P. (2009). Lyme neuroborreliosis: manifestations of a rapidly emerging zoonosis. *AJNR Am. J. Neuroradiol.* 30, 1079–1087. doi:10.3174/ajnr.A1579

Jacqmin, M., Herve, D., Viswanathan, A., Guichard, J. P., During, M., Dichgans, M., et al. (2010). Confluent thalamic hyperintensities in CADASIL. *Cerebrovasc. Dis.* 30, 308–313. doi:10.1159/000319607

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues Clin. Neurosci.* 15, 445–454.

Jokeit, H., Seitz, R., Markowitsch, H. J., Neumann, N., Ebner, A., and Witte, O. W. (1997). Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 120, 2283–2294. doi:10.1093/brain/120.12.2283

Joutel, A., Corpechot, C., Ducros, A., Vahedi, K., Chabriat, H., Mouton, P., et al. (1996). NOTCH3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 383, 707–710. doi:10.1038/383707a0

Joutel, A., Dodick, D. D., Parisi, J. E., Cecillon, M., Tournier-Lasserve, E., and Bousser, M. G. (2000). De novo mutation in the NOTCH3 gene causing CADASIL. *Ann. Neurol.* 47, 388–391. doi:10.1002/1531-8249(200003)47:3<388::AID-ANA19>3.3.CO;2-H

Kaplan, E., Goodglass, H., and Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia, PA: Lea and Febiger.

Kemp, J., Berthel, M. C., Dufour, A., Despres, O., Henry, A., Namer, I. J., et al. (2013). Caudate nucleus and social cognition: neuropsychological and SPECT evidence from a patient with focal caudate lesion. *Cortex* 49, 559–571. doi:10.1016/j.cortex.2012.01.004

Kessler, J., Markowitsch, H. J., and Denzler, P. (1990). *Der Mini-Mental-Status Test [The Mini-Mental-Status-Examination Test]*. Weinheim: Beltz-Test-Verlag.

Klein, S. B., and Gangi, C. E. (2010). The multiplicity of self: neuropsychological evidence and its implications for the self as a construct in psychological research. *Ann. N. Y. Acad. Sci.* 1191, 1–15. doi:10.1111/j.1749-6632.2010.05441.x

Kopelman, M. D., Wilson, B. A., and Baddeley, A. (1990). *The Autobiographical Memory Interview*. Bury St. Edmunds: Thames Valley Test Company.

Kroll, N., Markowitsch, H. J., Knight, R., and von Cramon, D. Y. (1997). Retrieval of old memories – the temporo-frontal hypothesis. *Brain* 120, 1377–1399. doi:10.1093/brain/120.8.1377

Lehrl, S. (2005). *Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) [Multiple Choice Lexis Intelligence Test]*. Balingen: Spitta Verlag.

Lezak, M. D. (1995). *Neuropsychological Assessment*. Oxford: Oxford University Press.

MacArthur, D. G., Manolio, T. A., Dimmock, D. P., Rehm, H. L., Shendure, J., Abecasis, G. R., et al. (2014). Guidelines for investigating causality of sequence variants in human disease. *Nature* 508, 469–476. doi:10.1038/nature13127

Manard, M., Carabin, D., Jaspar, M., and Collette, F. (2014). Age-related decline in cognitive control: the role of fluid intelligence and processing speed. *BMC Neurosci.* 15:7. doi:10.1186/1471-2202-15-7

Markowitsch, H. J. (1991). "Memory disorders after diencephalic damage: heterogeneity of findings," in *Memory Mechanisms: A Tribute to G. V. Goddard*, eds W. C. Abraham, M. C. Corballis, and K. G. White (Hillsdale, NJ: Lawrence Erlbaum Associates), 175–194.

Markowitsch, H. J., and Härting, C. (1996). Interdependence of priming performance and brain-damage. *Int. J. Neurosci.* 85, 291–300. doi:10.3109/00207459608986690

Markowitsch, H. J., Kalbe, E., Kessler, J., von Stockhausen, H.-M., Ghaemi, M., and Heiss, W.-D. (1999). Short-term memory deficit after focal parietal damage. *J. Clin. Exp. Neuropsychol.* 21, 784–796. doi:10.1076/jcen.21.6.784.853

Markowitsch, H. J., and Staniloiu, A. (2011). Amygdala in action: relaying biological and social significance to autobiographic memory. *Neuropsychologia* 49, 718–733. doi:10.1016/j.neuropsychologia.2010.10.007

Markowitsch, H. J., and Staniloiu, S. (2012). Amnesic disorders. *Lancet* 380, 1429–1440. doi:10.1016/S0140-6736(11)61304-4

Matsuda, O., and Saito, M. (1998). Crystallized and fluid intelligence in elderly patients with mild dementia of the Alzheimer type. *Int. Psychoger.* 10, 147–154. doi:10.1017/S1041610298005250

Mesulam, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann. Neurol.* 28, 597–613. doi:10.1002/ana.410280502

Metzinger, T. (2008). Empirical perspectives from the self-model theory of subjectivity: a brief summary with examples. *Prog. Brain Res.* 168, 215–245. doi:10.1016/S0079-6123(07)68018-2

Morris, J. C., Mohs, R. C., Rogers, H., Fillenbaum, G., and Heyman, A. (1988). Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol. Bull.* 24, 641–652.

Mykkanen, K., Junna, M., Amberla, K., Bronge, L., Kaariainen, H., Poyhonen, M., et al. (2009). Different clinical phenotypes in monozygotic CADASIL twins with a novel NOTCH3 mutation. *Stroke* 40, 2215–2218. doi:10.1161/STROKEAHA.108.528661

Mykkanen, K., Savontaus, M. L., Juvonen, V., Sistonen, P., Tuisku, S., Tuominen, S., et al. (2004). Detection of the founder effect in Finnish CADASIL families. *Eur. J. Hum. Genet.* 12, 813–819. doi:10.1038/sj.ejhg.5201221

Naylor, E., and Clare, L. (2008). Awareness of memory functioning, autobiographical memory and identity in early-stage dementia. *Neuropsychol. Rehabil.* 18, 590–606. doi:10.1080/09602010701608681

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex* 12, 313–324. doi:10.1016/S0010-9452(76)80035-4

Nelson, H. E. (1982). *National Adult Reading Test (NART)*. Windsor: NFER-Nelson.

Nyberg, L., Kim, A. S., Habib, R., Levine, B., and Tulving, E. (2010). Consciousness of subjective time in the brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 22356–22359. doi:10.1073/pnas.1016823108

Ogden, J. A. (1993). Visual object agnosia, prosopagnosia, achromatopsia, loss of visual imagery, and autobiographical amnesia following recovery from cortical blindness: case M.H. *Neuropsychologia* 31, 571–589. doi:10.1016/0028-3932(93)90053-3

Osterrieth, P. A. (1944). Le test de copie d´une figure complex: contribution à létude de la perception et de la mémoire [test of copying a complex figure: contribution to the study of perception and memory]. *Arch. Psychol.* 30, 286–356.

O'Sullivan, M., Ngo, E., Viswanathan, A., Jouvent, E., Gschwendtner, A., Saemann, P. G., et al. (2009). Hippocampal volume is an independent predictor of cognitive performance in CADASIL. *Neurobiol. Aging* 30, 890–897. doi:10.1016/j.neurobiolaging.2007.09.002

O'Sullivan, M., Singhal, S., Charlton, R., and Markus, H. S. (2004). Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. *Neurology* 62, 702–707. doi:10.1212/01.WNL.0000113760.72706.D2

Parisi, V., Pierelli, F., Fattapposta, F., Bianco, F., Parisi, L., Restuccia, R., et al. (2003). Early visual function impairment in CADASIL. *Neurology* 60, 2008–2010. doi:10.1212/01.WNL.0000070411.13217.7E

Parisi, V., Pierelli, F., Malandrini, A., Carrera, P., Olzi, D., Gregori, D., et al. (2000). Visual electrophysiological responses in subjects with cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Clin. Neurophysiol.* 111, 1582–1588. doi:10.1016/S1388-2457(00)00366-7

Parkin, A. J., and Java, R. I. (1999). Deterioration of frontal lobe function in normal aging: influences of fluid intelligence versus perceptual speed. *Neuropsychology* 13, 539–545. doi:10.1037/0894-4105.13.4.539

Perneczky, R., Pohl, C., Bornschein, S., Forstl, H., Kurz, A., and Diehl-Schmid, J. (2009). Accelerated clinical decline in well-educated patients with frontotemporal lobar degenerations. *Eur. Arch. Psychiatry Clin. Neurosci.* 259, 362–367. doi:10.1007/s00406-009-0004-6

Peters, N., Opherk, C., Danek, A., Ballard, C., Herzog, J., and Dichgans, M. (2005). The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. *Am. J. Psychiatry* 162, 2078–2085. doi:10.1176/appi.ajp.162.11.2078

Reinhold, N., and Markowitsch, H. J. (2007). Emotion and consciousness in adolescent psychogenic amnesia. *J. Neuropsychol.* 1, 53–64. doi:10.1348/174866407X180819

Reitan, R. (1958). Validity of the trail making test as an indication of organic brain damage. *Percept. Mot. Skills* 8, 271–276. doi:10.2466/PMS.8.7.271-276

Rieger, B., and Markowitsch, H. J. (1996). Implicit and explicit mnestic performance of patients with prefrontal, medial temporal, and basal ganglia damage. *Neurol. Psychiatr. Brain Res.* 4, 53–74.

Roos, K. L., and Berger, J. R. (2007). Is the presence of antibodies in CSF sufficient to make a definitive diagnosis of Lyme disease? *Neurology* 69, 949–950. doi:10.1212/01.wnl.0000271901.94853.24

Rufa, A., Malandrini, A., Dotti, M. T., Berti, G., Salvadori, C., and Federico, A. (2005). Typical pathological changes of CADASIL in the optic nerve. *Neurol. Sci.* 26, 271–274. doi:10.1007/s10072-005-0470-1

Russell, M. B. (2010). Genetics of dementia. *Acta Neurol. Scand.* 190, 58–61. doi:10.1111/j.1600-0404.2010.01377.x

Sabbadini, G., Francia, A., Calandriello, L., Di Biasi, C., Trasimeni, G., Gualdi, G. F., et al. (1995). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). Clinical, Neuroimaging, pathological and genetic study of a large Italian family. *Brain* 118, 207–215. doi:10.1093/brain/118.1.207

Savage, C. R., Baer, L., Keuthen, N. J., Brown, H. D., Rauch, S. L., and Jenike, M. A. (1999). Organizational strategies mediate nonverbal memory impairment in obsessive-compulsive disorder. *Biol. Psychiatry* 45, 905–916. doi:10.1016/S0006-3223(98)00278-9

Scarmeas, N., Albert, S. M., Manly, J. J., and Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatr.* 77, 308–316. doi:10.1136/jnnp.2005.072306

Schmidtke, K., Manner, H., Kaufmann, R., and Schmolck, H. (2002). Cognitive procedural learning in patients with fronto-striatal lesions. *Learn. Mem.* 9, 419–429. doi:10.1101/lm.47202

Seidl, U., Markowitsch, H. J., and Schröder, J. (2006). "Die verlorene Erinnerung. Störungen des autobiographischen Gedächtnisses bei leichter kognitiver Beeinträchtigung und Alzheimer-Demenz," in *Warum Menschen sich erinnern können. Fortschritte in der Interdisziplinären Gedächtnisforschung [Why Human Beings can Remember. Progress in Interdisciplinary Memory Research]*, eds H. Welzer and H. J. Markowitsch (Stuttgart: Klett), 286–302.

Shadick, N. A., Phillips, C. B., Sangha, O., Logigian, E. L., Kaplan, R. F., Wright, E. A., et al. (1999). Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. *Ann. Intern. Med.* 131, 919–926. doi:10.7326/0003-4819-131-12-199912210-00003

Smith, G. E., Pankratz, V. S., Negash, S., Machulda, M. M., Petersen, R. C., Boeve, B. F., et al. (2007). A plateau in pre-Alzheimer memory decline: evidence for compensatory mechanisms? *Neurology* 69, 133–139. doi:10.1212/01.wnl.0000265594.23511.16

Smith, S. J., Souchay, C., and Conway, M. A. (2010). Overgeneral autobiographical memory in Parkinson's disease. *Cortex* 46, 787–793. doi:10.1016/j.cortex.2009.08.006

Souchay, C., Guillery-Girard, B., Pauly-Takacs, K., Wojcik, D. Z., and Eustache, F. (2013). Subjective experience of episodic memory and metacognition: a neurodevelopmental approach. *Front. Behav. Neurosci.* 7:212. doi:10.3389/fnbeh.2013.00212

Souchay, C., and Smith, S. J. (2013). Autobiographical memory in Parkinson's disease: a retrieval deficit. *J. Neuropsychol.* 7, 164–178. doi:10.1111/jnp.12014

Spitz, H. H., Webster, N. A., and Borys, S. V. (1982). Further studies of the Tower of Hanoi problem-solving performance of retarded young adults and nonretarded children. *Dev. Psychol.* 18, 922–930. doi:10.1037/0012-1649.18.6.922

Spreen, O., and Strauss, E. (1998). *A Compendium of Neuropsychological Tests*, 2nd Edn. New York: Oxford University Press.

Stanek, G., Wormser, G. P., Gray, J., and Strle, F. (2012). Lyme borreliosis. *Lancet* 379, 461–473. doi:10.1016/S0140-6736(11)60103-7

Staniloiu, A., Borsutzky, S., Woermann, F., and Markowitsch, H. J. (2013). Social cognition in a case of amnesia with neurodevelopmental mechanisms. *Front. Psychol.* 4:342. doi:10.3389/fpsyg.2013.00342

Staniloiu, A., and Markowitsch, H. J. (2012). "The splitting of the brain: a reorientation towards fiber tracts damage in amnesia," in *Brain Damage: Causes, Management, and Prognosis*, eds A. J. Schäfer and J. Müller (Hauppauge, NY: Nova Science Publishers), 41–70.

Steere, A. C., Sikand, V. K., Schoen, R. T., and Nowakowski, J. (2003). Asymptomatic infection with *Borrelia burgdorferi*. *Clin. Infect. Dis.* 37, 528–532. doi:10.1086/376914

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460. doi:10.1017/S1355617702813248

Stone, J., Smyth, R., Carson, A., Warlow, C., and Sharpe, M. (2006). La belle indifférence in conversion symptoms and hysteria: systematic review. *Br. J. Psychiatry* 188, 204–209. doi:10.1192/bjp.188.3.204

Teichner, G., and Wagner, M. T. (2004). The test of memory malingering (TOMM): normative data from cognitively intact, cognitively impaired, and elderly patients with dementia. *Arch. Clin. Neuropsychol.* 19, 455–464. doi:10.1016/S0887-6177(03)00078-7

Tombaugh, T. N. (1996). *Test of Memory Malingering (TOMM)*. New York: Multi Health Systems.

Tournier-Lasserve, E., Iba-Zizen, M. T., Romero, N., and Bousser, M. G. (1991). Autosomal dominant syndrome with strokelike episodes and leukoencephalopathy. *Stroke* 22, 1297–1302. doi:10.1161/01.STR.22.10.1297

Tournier-Lasserve, E., Joutel, A., Melki, J., Weissenbach, J., Lathrop, G. M., Chabriat, H., et al. (1993). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nat. Genet.* 3, 256–259. doi:10.1038/ng0393-256

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–403.

Tulving, E. (2005). "Episodic memory and autonoesis: uniquely human?," in *The Missing Link in Cognition: Evolution of Self-Knowing Consciousness*, eds H. Terrace and J. Metcalfe (New York: Oxford University Press), 3–56.

Valenti, R., Salvadori, E., Pescini, F., Poggesi, A., Castellini, G., Antonini, S., et al. (2013). Facial affect recognition in CADASIL patients. *Arch. Clin. Neuropsychol.* 28, 65–71. doi:10.1093/arclin/acs097

van Bogaert, L. (1955). Encephalopathie sous-corticale progressive (Binswanger) a evolution rapide chez deux soeurs. *Acta Med. Hell.* 24, 961–972.

Van der Aa, N., Vandeweyer, G., and Kooy, R. F. (2010). A boy with mental retardation, obesity and hypertrichosis caused by a microdeletion of 19p13.12. *Eur. J. Med. Genet.* 53, 291–293. doi:10.1016/j.ejmg.2010.05.006

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* 7, 1271–1278. doi:10.1038/nn1341

Wagner, A. D., Shannon, B. J., Kahn, I., and Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn. Sci.* 9, 445–453. doi:10.1016/j.tics.2005.07.001

Wilson, R. S., Barnes, L. L., Aggarwal, N. T., Boyle, P. A., Hebert, L. E., Mendes de Leon, C. F., et al. (2010). Cognitive activity and the cognitive morbidity of Alzheimer disease. *Neurology* 75, 990–995. doi:10.1212/WNL.0b013e3181f25b5e

Yamamoto, Y., Craggs, I., Baumann, M., Kalimo, H., and Kalaria, R. N. (2011). Molecular genetics and pathology of hereditary small vessel diseases of the brain. *Neuropathol. Appl. Neurobiol.* 17, 94–113. doi:10.1111/j.1365-2990.2010.01147.x

Zeman, A., McLean, B., Keir, G., Luxton, R., Sharief, M., and Thompson, E. (1993). The significance of serum oligoclonal bands in neurological diseases. *J. Neurol. Neurosurg. Psychiatr.* 56, 32–35. doi:10.1136/jnnp.56.1.32

Zieren, N., Duering, M., Peters, N., Reyes, S., Jouvent, E., Herve, D., et al. (2013). Education modifies the relation of vascular pathology to cognitive function: cognitive reserve in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Neurobiol. Aging* 34, 400–407. doi:10.1016/j.neurobiolaging.2012.04.019

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The neuroscience of face processing and identification in eyewitnesses and offenders

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Humans are experts in face perception. We are better able to distinguish between the differences of faces and their components than between any other kind of objects. Several studies investigating the underlying neural networks provided evidence for deviated face processing in criminal individuals, although results are often confounded by accompanying mental or addiction disorders. On the other hand, face processing in non-criminal healthy persons can be of high juridical interest in cases of witnessing a felony and afterward identifying a culprit. Memory and therefore recognition of a person can be affected by many parameters and thus become distorted. But also face processing itself is modulated by different factors like facial characteristics, degree of familiarity, and emotional relation. These factors make the comparison of different cases, as well as the transfer of laboratory results to real live settings very challenging. Several neuroimaging studies have been published in recent years and some progress was made connecting certain brain activation patterns with the correct recognition of an individual. However, there is still a long way to go before brain imaging can make a reliable contribution to court procedures.

Keywords: eyewitness memory, eyewitness testimony, face processing, offender's memory, identification, fMRI, real-life events, brain imaging

INTRODUCTION

Our face is a very salient part of our body and maybe the most memorable feature (Henke et al., 1994). We are able to remember a great amount of individual faces. Our sensitivity for the small differences between facial characteristics is higher than for any other object category (O'Toole, 2005). This is one of the reasons why face recognition does play such a fundamental role for identification of a culprit. This applies a fortiori, as faces are less alterable than clothes or even hair styles.

Since eyewitnesses yield crucial and sometimes even the only available evidence in court, their testimonies are of critical importance for the juridical system. Unfortunately, eyewitnesses' memories are not immune to decay and distortions. In an investigation of several cases in which convicts had been exonerated by DNA evidence afterward, the National Institute of Justice asserted that mainly eyewitness testimonies had been the most compelling evidence (Connors et al., 1996). Although in some cases eyewitnesses might have deceitful intentions and even give false confessions (e.g., to protect themselves or others), false information is often provided inadvertently for reasons of memory distortion. Our memories can vanish partly or completely, can be deformed in many ways or entirely originate from illusion (Markowitsch and Staniloiu, 2012). But not only eyewitnesses' memories are prone to distortion. Offenders' memories can be modified by different factors, as well. Although in most cases face identification made by the offender is of less importance, it can become relevant given that eyewitnesses might misidentify a person as a culprit or in some cases might have deceitful intentions. For those reasons, memories of an offender are fundamental for his or hers defense. Furthermore, some evidence concerning deviated face processing in offenders could be obtained in recent years, concluding that faces are processed differently even during non-criminal events, as well as facial expressions (Pardini and Phillips, 2010). A better comprehension of altered brain activity in culprits might give an expedient contribution to the understanding of delinquent behavior.

For literature search and selection, we started with standard databases like PubMed, PsycInfo, and Web of Science and used a large quantity of different key words in order to receive the relevant literature for this article. The most fruitful ones have been amongst others: *eyewitness*, *face processing*, *face recognition*, *functional magnetic resonance imaging (fMRI)*, *identification*, *offender*, and different combinations of these. Secondly, we also used the "related article" and "cited by" search. We decided not to restrict ourselves too strongly by this common approach and included some articles which were obtained differently but contributed significantly to our topic as well as a few book chapters. Selection criteria were currentness of data, meeting the methodological demands, and topic relatedness. For other domains like memory influencing factors in the introduction, we conducted a separate literature search using other keywords, mainly *memory* in combination with different terms like *alcohol*, *age*, *amnesia*, *attention*, *context dependent*, *emotion*, *false memory*, *intoxication*, *stress*, and *trustworthiness*.

By reviewing the eminent literature we will (a) give an introduction to the general factors that can affect memory storage and retrieval in eyewitnesses and offenders, with an excursus on their treatment in police investigations; (b) comprise in particular which brain areas are involved in face recognition and how such correlates are influenced by internal and external factors; (c)

explore the role of face processing, memory distortions, and deceit in offenders; (d) examine the comparability of data obtained in a laboratory environment to actual events and (e) conclude by discussing the relevance of these findings for juridical purposes, while providing a perspective on the challenges that still lie ahead.

FALSE MEMORIES

Next to incomplete memory encoding and memory loss, the creation of false memories poses a considerable challenge for lawyers and experts. The term "false memory" refers to the recollection of an event that has actually been experienced differently or even not at all (Kühnel and Markowitsch, 2009). While memory loss usually works for the benefit of the culprit, false memories can lead to wrong convictions and imprisonment of innocent people (Busey and Loftus, 2007). They are a normal everyday phenomenon, but have serious consequences in court. When talking about eyewitnesses in the following, we have to keep in mind that offenders are also eyewitnesses to a certain extent and many memory influencing factors apply for their memories as well. Brainerd and Reyna (2005) reported a case of a man who after a suggestive police interview accused himself of murdering is infant son. Later evidence given by experts who assumed that the injuries were not likely to be caused in the way the accused had described and recordings of the police interview led to the assumption that the confession was coerced. Though false memories appear regularly, certain conditions can enhance their occurrence. In police interviews, caution is indicated, as eyewitnesses can be very prone to suggestions (Loftus, 2011). This may be promoted by the mental or physical constitution of the eyewitness (for example high emotional state, stress, or sleep-deprivation) or social demands like the wish to help the police and to catch the culprit. Zhu et al. (2010) also reported individual differences in false memory concerning the exposure to misinformation. They found a negative correlation with intelligence, perception, memory, and face judgment abilities. Misinformation can be obtained by conversation with other eyewitnesses or by suggestive questions during the police interview. Suggestive questions can include false or at least new information for the eyewitness. They can also facilitate the creation of false memories without providing any new content, for example by presuming that the eyewitness must have observed something (Brainerd and Reyna, 2005). However, questioning cannot only provoke false memories, but it can also induce forgetting (Migueles and García-Bajos, 2007; Camp et al., 2012). Retrieval practice normally enhances recollection of the studied items, but it can have opposite effects on related but not recapitulated information. This phenomenon has been observed with respect to, for example, the memory of offender's characteristics. A multitude of factors affects eyewitnesses' memory, such as the wording of questions, post-event information, confidence malleability, attitudes and expectations, exposure time, presentation format, or alcohol intoxication (Kassin et al., 2001).

Though guidelines for the treatment of eyewitnesses do exist (Technical Working Group for Eyewitness Evidence, 2003), Wright (2007) gave voice to his concern that jurors might not be aware of the differences between presentation formats for offender identification (e.g., sequential and simultaneous lineups) and their reliability. Apparently, not only eyewitnesses and suspects have to be handled with care for preserving their memories, but also judges, advocates, and jurors must be sensitized to possible memory influencing factors.

INFLUENCES ON MEMORY ACCURACY AND QUANTITY

Memory performance can be influenced by many different factors. Below we highlight some of those memory enhancing or impairing variables, although we cannot assume the possibility of giving an exhausting overview.

Age is one important factor that affects memory of events. Infantile eyewitnesses pose a special challenge to investigators, inasmuch as they are more susceptible to suggestions and research approaches are limited for ethical reasons. In a group of children aged 5–12 years old, older children were more prone to connect gist-based information across several events than younger children (Odegard et al., 2009). Clifford et al. (2012), who compared 7- to 8-year-olds with a group of 13- to 14-year-olds, also found the younger children to be more vulnerable to the detrimental effects of time delay in an identification task. In a study conducted by Humphries et al. (2012), adults made more correct identifications in the sequential lineup video condition than 5- to 6-year-olds and 9- to 10-year-olds, but not in the simultaneous and in elimination lineups. During target-absent lineups, adults exhibited higher correct rejection rates than children, regardless of lineup condition. At the upper end of the age range, findings are quite mixed. Elderly persons (aged 57–73) tended to make more false alarms than younger adults (aged 19–27) in an experiment by García-Bajos et al. (2012). They also performed poorer in a recall task, but only regarding actions untypical for the event (i.e., a bank robbery, a video of which had been shown to the participants). Nevertheless, there was no difference in recall between groups concerning highly typical actions. Notwithstanding lower recall scores, elderly persons seem to be less prone to misinformation effects under special circumstances. In an experiment by West and Stone (2013) younger adults made more mistakes due to misinformation than older adults when learning occurred incidentally, but not when it was intended. Maybe less complete information processing in the older group might have worked in this case to their benefit. Given these results, it can be concluded, that although differences exist between older and younger adults' memory abilities, they may be more or less pronounced depending on the exact investigated skills.

The capability of identifying unfamiliar faces varies largely over individuals, and we still do not completely understand the underlying mechanisms. Megreya and Bindemann (2013) investigated the relationship between identification abilities and personality and found higher identification skills for women who scored low on anxiety and tension and high on emotional stability. The impact of personality on eyewitness testimony is still unclear, but although findings are still somehow heterogeneous, our understanding of other modulating factors is much less limited.

Most studies dealing with the influences of alcohol on eyewitness memory report alcohol intoxication to cause reduced recall accuracy (van Oorsouw and Merckelbach, 2012) as well as impairment of conscious recollection (Ray and Bates, 2006). However, familiarity-based recollection seems to be not affected (Bisby et al., 2010). Regarding the recognition of perpetrators, these findings

imply that identification ability in lineups or photospreads in which the culprit is present is apparently not impaired by alcohol consumption, although it comes to more false identifications in culprit-absent trials (Yuille and Tollestrup, 1990; Dysart et al., 2002). Read et al. (1992) found that alcohol reduced person identification in a consecutive study, but only when participants' arousal was low. In contrast, Schreiber Compo et al. (2012) could not find a significant difference between the amount of accurate or inaccurate details (as well as "I don't know" statements) reported by sober and intoxicated participants. However, under certain circumstances, alcohol might even benefit memory. In a study by Moulton et al. (2005), alcohol administered after learning facilitated recall of prose passages read before. Perhaps alcohol preserves recently acquired memories by suppressing cognitive interference with new material. The impact of alcohol on eyewitness testimony may therefore depend on the timing of consumption. Interestingly, numerous studies have been performed since many decades that revealed state-dependent recall under alcohol (e.g., Goodwin et al., 1969; Hoffman et al., 1997). Weingartner et al. (1976) for instance found that encoding under alcohol intoxication should be followed by retrieval under alcohol intoxication. If individuals are sober at retrieval while they had learned the words while intoxicated, they performed poorer than in the matched condition. In any case, alcohol intoxication in witnesses during the incident seems to be widespread. Astonishingly, only few general guidelines for interviewing intoxicated eyewitnesses exist (Evans et al., 2009b), so that sober and intoxicated eyewitness are often treated quite similarly (Palmer et al., 2013). Nevertheless, the results of an experiment conducted by Evans and Schreiber Compo (2010) are somehow more encouraging: even if participants did not consider the whole range of potential factors and their interactions, they were quite aware of possible derogating effects of alcohol on eyewitnesses' cognitive abilities and these considerations modulated their verdicts. But for including such considerations, jurors must be informed about possible intoxications and according to Evans et al. (2009b), 71% of the investigators do not use an instrument for determining the breath alcohol content when intoxication is suspected. This illustrates the need for standardized guidelines.

Results concerning the impact of stress on eyewitness memory are diverse as well. Stress can enhance memory for central events, especially in comparison to peripheral events, if stimuli are encoded under arousal and stress is experienced shortly after encoding (McGaugh and Roozendaal, 2002; Echterhoff and Wolf, 2012; McGaugh, 2013). Cahill et al. (2003) found a beneficial effect of post-learning stress on emotionally arousing stimuli but not on neutral items. Other studies argue for more detrimental effects of stress. In two studies described by Wolf et al. (2004), cortisol administration had more detrimental effects on the retrieval of neutral autobiographic episodes, while it impaired retrieval of emotional words from a word list (cf. Kuhlmann et al., 2005; de Quervain et al., 2007). The way in which stress affects memory for emotional content, seems to depend on the kind of stimuli learned. Kuhlmann and Wolf (2006) observed stress-induced recall enhancement for emotional pictures and an impairment for neutral pictures while recognition remained unaffected (cf. Liu et al., 2008). Stress can also exacerbate the misinformation effect (Morgan et al., 2013) and stress during encoding can lead to a more liberal response bias (Qin et al., 2012). Participants completing a high-intensity physical-assault exercise before encoding showed impaired performance in recall and recognition. They were also less able to identify a target in a lineup (Valentine and Mesout, 2009; Hope et al., 2012). Andreano and Cahill (2006) found an inverted-U relationship between dose of endogenous stress hormones and memory in men but not in women. Hence, stress intensity might also contribute to enhancing and impairing effects of stress. Furthermore, stress also modulates the extent of involvement of several brain structures (Schwabe and Wolf, 2012). In summary, the effect of stress on memory depends on many parameters like gender, stress intensity, emotional valence, time between learning and retrieval, context (Schwabe et al., 2009), time of stress induction (Smeets et al., 2008; Wolf, 2012), stimuli material, and its relatedness to the stressor (Smeets et al., 2009).

Several studies have been conducted concerning context-dependent memory. Congruence between the context of a perceived event and the retrieval situation can enhance memory for this event (cf. Smith and Vela, 2001 for a review). Context can refer, e.g., to the physical environment (Godden and Baddeley, 1975) or to the physiological state like intoxication (Eich, 1980) but also to the experienced mood during learning phase and retrieval phase (Fitzgerald et al., 2011).

One phenomenon with impact on our attention and therefore on our memory is referred to as "weapon focus." Negative arousing objects in a scene (e.g., weapons) can reduce recognizability of peripheral information (Easterbrook, 1959; Kensinger and Schacter, 2007; Kensinger et al., 2007; Waring and Kensinger, 2009). In general, memory for details of negative arousing stimuli seems to be enhanced compared to neutral objects (Kensinger et al., 2006). On the other hand, emotionally aversive stimuli can disrupt later recall of previously retrieved neutral information (Strange et al., 2003, 2010). Interestingly, Hurlemann et al. (2005) could not only demonstrate negative items to elicit retrograde amnesia for preceding neutral words, but also found positive stimuli to induce hypermnesia for previously recapitulated neutral items. They also observed emotionally arousing stimuli – negative items as well as positive items – to provoke anterograde amnesia. Thus, valence and arousal seem to make different contributions to memory, with valence determining enhancing or impairing effects on retrograde memory and arousal affecting anterograde memory (Hurlemann, 2006). But the experience of an aversive event cannot only induce amnesia, it can also lead to anxiety disorders like post-traumatic stress disorder (PTSD) (Mineka and Oehlberg, 2008).

The influences discussed above rather concern general memory abilities and possible influencing factors. Below we now will address the more specific field of face recognition and the underlying neuronal processes.

MEMORY AND FACE PROCESSING IN EYEWITNESSES

Because humans are better able to distinguish between faces than between objects of any other category, this expertise in face processing led to a wide discussion about the existence of specialized brain areas which are solely responsible for face processing (Sato and Yoshikawa, 2013). A lot of light was shed by the examination of patients with *prosopagnosia*, an inability of identifying previously known persons by watching their faces (Damasio et al., 1990;

Minnebusch et al., 2009). Typically these patients remain capable of recognizing relatives and friends from voice, categorizing faces as faces, and are often even able to interpret facial expressions (Tranel et al., 1988).

We have to consider that face recognition involves a lot of different processes. In the eyewitness context, the aim is to distinguish between familiar und unfamiliar faces *(Have you seen this man before?)*, or even better: to ascertain a special identity of a person *(Is this the man who offended you?)*. But a lot of variables modulate the way in which faces are analyzed, like the individual components of the face (Itier et al., 2006), race (Phelps et al., 2000; Behrman and Davey, 2001; Golby et al., 2001; Johnson and Frederickson, 2005; Turk et al., 2005), sex (Lewin and Herlitz, 2002; Rahman et al., 2004; Hofmann et al., 2006; Rehnman and Herlitz, 2007; McBain et al., 2009), expressed mood (Kaufmann and Schweinberger, 2004; Schulte-Rüther et al., 2007), movement (Roark et al., 2003; Lander and Davies, 2007), and the eyewitness' age (Memon et al., 2003a; Firestone et al., 2007). Likewise, hair does have an effect on eyewitness accuracy (Wright and Sladden, 2003; Frowd et al., 2012c), but is often excluded from face recognition studies which might be wise also in respect of delinquents often wearing headgears.

Face processing always seems to cause activation in the face fusiform regions, but encoding and recall of learned faces must utilize more extended networks (Elgar and Campbell, 2001; Steeves et al., 2006; Lee et al., 2012; Parvizi et al., 2012), like participation of the anterior temporal cortex including the anterior tip of the collateral sulcus (Nestor et al., 2011; Nasr and Tootell, 2012). Rossion et al. (2012) used intact and scrambled versions of object and face pictures to unravel the neural mechanisms behind face processing in an fMRI block design experiment. They identified several clusters: e.g., in the pulvinar, inferior occipital gyrus, posterior superior temporal gyrus, anterior infero-temporal cortex, and amygdala, all with a pronounced right lateralization. The middle fusiform gyrus distinguished best between faces and objects but because of its concomitant differentiation between the pictures of cars and scrambled cars it was also identified as the least face-selective region of the ones mentioned above.

Even the kind of familiarity we experience while watching a face, the way in which we became acquainted with someone, does play a role. The processing of famous faces in comparison to personally familiar faces involves different brain areas (Sugiura et al., 2011). Von Der Heide et al. (2013) included 25 fMRI studies in a meta-analysis dealing with famous faces and familiar faces stimuli and also conducted an own empirical fMRI experiment with picture stimuli of faces differing in famousness and personal relationship. Baseline images consisted of blurred and landmark pictures. The authors found higher left-lateralized anterior temporal lobe activations for familiar faces, while activation associated with novel individuals was evoked in the right anterior temporal lobe. Activation connected to personally familiar faces and famous faces partially overlapped, but famous faces activation exhibited a more ventral pattern. The study design is somehow problematic as experimental tasks differed between famous and familiar faces. For familiar faces, participants rated which of two presented known persons they feel closer to, while in the famous faces condition, participants had to complete a 0-back task indicating if two images of the same category (famous vs. non-famous) appeared in succession. But it can be concluded that any of the mentioned aspects above, like the individual characteristics of face components and their relation to each other, evoke slightly different combinations of neural collaboration. This is one of the reasons why clarifying the underlying neural mechanisms is so demanding. For a holistic understanding, face recognition has to be broken down to many single processes, which probably do not stand for themselves, but depend on each other.

From a criminological perspective, the most intriguing aspects are: (i) the distinction between familiar and unfamiliar (Shah et al., 2001) and (ii) the precise source, i.e., where, when, and under what circumstances someone has been seen before. The first issue was addressed by Gobbini and Haxby (2006) who compared the neural responses to known faces with activation corresponding to new faces in an event-related fMRI study. Familiarity of known faces was induced experimentally in order to avoid any biographical or emotional content. The authors found higher activation in the precuneus while watching familiar faces. Observing new faces led to higher responses in the fusiform gyrus and the amygdala. The authors suggested that this might reflect higher encoding effort (or increased attentional load) and an elevated guarding function, respectively. In a preceding fMRI study (Gobbini et al., 2004), similar results have been found with the amygdala showing lower activation during presentation of personal familiar faces compared to famous familiar faces and faces of strangers. New faces were associated with higher activation in the fusiform gyrus in contrast to famous familiar faces. But no difference between faces of strangers and faces of personally acquainted persons was detected in this region. Familiarity's effect on this area does not seem to be linear. Gobbini and Haxby (2007) also proposed a new model for face recognition consisting of the three elemental parts "visual appearance," "person knowledge" (e.g., information about traits, intentions, attitudes, biographical facts, and episodic memories), and the "emotional response." These components may involve different brain structures and failure to access one of them could lead to impaired recognition. The emotional response to the face of an offender will obviously differ from the reaction to beloved relatives or friends and consequently alter brain activation. Unrestricted transferability from those findings to criminal contexts is indeed questionable. To untangle the underlying neural mechanisms involved in recognition of a culprit's face, we have to investigate more realistic settings which exhibit criminal content. But before we have a closer look on studies facing this issue, we must keep in mind that several methods and approaches exist to confront eyewitnesses with suspects or rather to extract the wanted facial details from their memories: like lineups (Clark and Tunnicliff, 2001; Wells and Olson, 2003), showups, photospreads (Yarmey, 2004), mug shots, or facial-composite production (Wells and Hasel, 2007). It is rather obvious that these different procedures do not only lead to different results in memory accuracy, but will also affect the incidental brain activity. Furthermore, there is evidence that the amygdala is active toward attractiveness of a face, particularly its eyes (Demos et al., 2008) and that individuals – such as boys with conduct problems and callous-unemotional traits – may be unable to detect the emotional expression of a face due to amygdala hypoactivity (Jones et al., 2009). Adolphs et al. (1998)

also found three subjects with complete bilateral amygdala damage to judge faces as more trustworthy and approachable than healthy individuals. These findings are in accord with the results obtained by Winston et al. (2002) who could also show in an event-related fMRI study the bilateral amygdala to be involved in ratings of faces as untrustworthy, as well as the right insula, while activation in the right superior temporal sulcus was correlated with judgments as trustworthy.

Lefebvre et al. (2007) measured event-related brain potentials in culprit present and absent lineup tasks at different levels of time delay. Participants first watched four videos, all showing a mock burglary incident. They were also instructed to pretend that they had observed a real crime, for which they were the only witnesses. Although memory accuracy deteriorated over time, P300 remained a reliable predictor for correct identification. In culprit-absent lineups, P300 was reduced. It would indeed be desirable to extract information about the identity of a culprit even when the eyewitness is unaware of the correct features. Aspiring to make a contribution to this issue, Iiadaka et al. (2012) induced false memories in a face recognition fMRI experiment. The authors used morphed pictures of faces to evoke a false familiarity for lure faces. During the test phase, participants were confronted with old, new, and lure targets in a randomized order. Feelings of familiarity were correlated to activation in the orbital cortices, as well as to neural response in the left amygdala. Here, activity was highest for correct responses, lowest for incorrect answers regarding old and new items. Neural reaction to incorrect answers concerning lure items (i.e., stating a lure item as old) and therefore related to false memories fell somewhere in between. A participation in false memories could be unveiled in a region in the anterior cingulate cortex. In this area, activation was correlated with the difference in reaction times observed for lure items. Very demanding is the question what happens when we misinterpret a face as familiar while the accordant person is unknown to us. Do we only mix up similar characteristics of two faces as it would be true for the lure items? Moreover, incorrect answers to completely new faces could be just as illuminating. Unfortunately, although Iiadaka et al. (2012) recorded participants' confidence ratings (indicating how sure they feel about their responses), the authors could not differentiate between certainty statements due to a lack of answers expressed with high confidence (cf. Risius et al., 2013).

We must bear in mind our objective is not only to help eyewitnesses remember correctly and avoid the creation of false memories, but that eyewitnesses can also be deceitful for a variety of reasons (e.g., to protect themselves or others). Bhatt et al. (2009) conducted an fMRI study in which participants were confronted with target present and target absent photo lineups. Targets had been learned previously. The subjects were partly instructed to lie and to conceal the identity of the learned face and to pretend that another face is the recognized one. During the truthful trials, it was their task to identify the known face and to pick any if no face seemed familiar to them. Lying was correlated with activation in the medial frontal gyrus, red nucleus, inferior frontal gyrus, supramarginal gyrus, superior frontal gyrus, dorsolateral prefrontal cortex (all occurring right-lateralized), and the bilateral precuneus.

As the entirety of the studies presented above clearly shows, we are not just dealing with one distinct network for face recognition but rather with a set of different brain areas that are more or less involved depending on the precise face processing demands. We thus have to face the far more difficult task of unraveling a multitude of interactions. While a complete understanding of face recognition on a neural level will probably elude us for quite a while, some neural correlates allow at least for a certain degree of predictability in a specialized setting.

MEMORY AND FACE PROCESSING IN OFFENDERS

Since we began to discuss the possibility of eyewitnesses operating as delinquents, we must be aware of the fact that offenders are eyewitnesses as well and that it is of high juridical interest to learn about their contingent memory specifics. However, whereas the mechanisms of face recognition are of particular interest in eyewitness testimony, they are not in the focus of attention in offender's memory. Nonetheless, some insight could be gained referring to altered brain activation during face processing in offenders, for instance regarding emotional expressions as has been demonstrated in a couple of studies. In a case-report paradigm, Hoff et al. (2009) collected fMRI data from a psychopath with criminal background and a control group performing an *n*-back task with drawn facial expressions and scrambled drawings. The researchers found pronounced differences between groups: facial expressions involved phylogenetically older regions in the psychopathic participant, whereas only neocortical areas were activated in the control group. In another fMRI study, subjects labeled the sex of male and female faces with differing emotional expressions in varied intensities (Pardini and Phillips, 2010). Participants were chronically violent or non-violent men. The former showed reduced brain activation in the dorsomedial prefrontal cortex referring to faces in general, regardless of the expressed mood. In contrast, higher activation emerged in these regions with respect to mild fearful faces. The group of violent men also exhibited higher activation in the amygdala for neutral in comparison to happy faces. Very remarkable is the finding of an elevated activation for mild fearful faces in the violent group which could not be seen while watching neutral faces or faces with more pronounced fearful cues. The authors suggest that chronically violent men may interpret ambiguous facial expressions differently from others.

Criminals often exhibit mental disorders like addiction, amnesia, or psychopathy, and those characteristics could be also responsible for alternating results in memory or brain function (Parwatikar, 1990; Markowitsch and Staniloiu, 2011; Oszoy et al., 2013). In a word and face encoding fMRI experiment for example, alcohol-dependent patients did not exhibit the right-lateralized activation in the parahippocampal region during face encoding which had been observed in a healthy control group (Yoon et al., 2009). Concerning the immediate effects of alcohol on memory encoding, Söderlund et al. (2007) reported alcohol impaired memorization for object pairs and face-name pairs (but not for words and phrase-word pairs) that was associated with reduced bilateral prefrontal activation (cf. also the above-mentioned investigations on the state-dependency of memory under alcohol influence). Other differences between groups were found in the parahippocampal gyrus. In cases of antisocial personality disorder,

discrepancies in brain function have been observed as well. In an EEG study by Pfabigan et al. (2012) with happy and angry faces as feedback stimuli, participants with antisocial personality traits displayed a smaller event-related P1 amplitude than participants with low antisocial personality scores.

Although face identification by offenders is of less juridical importance, comprehension of those distorted processes and influences on memory might lead to a better understanding of offender behavior. Usually, the more intriguing question in this context concerns the details of the crime, which may include the description of the victim but mostly highlight the act and circumstances of the perpetration. A deeper understanding of brain functions dealing with the representation, encoding, and recall of event memory would make an important contribution. Hasson et al. (2004) used functional brain imaging to demonstrate parallels in brain activation between subjects watching a movie. They found intersubject synchronization in multiple cortical regions. The results lead to the assumption that identical events might be processed in a similar way in different individuals. However, is this conferrable to criminal events? Offender and victim (to a certain extent) experience the same incident, but their particular role, their thoughts, and emotions will obviously be totally different from each other. While a crime in many cases is mostly traumatic for victims, possible occurrence of pleasurable feelings is also discussed in offenders (Evans, 2006). But although research normally focuses on trauma in victims, offenders can also suffer from intrusive memories related to their crimes and even develop a PTSD (Evans et al., 2007b). It is difficult to make a statement concerning prevalence, and indications vary in a wide range over studies (Evans, 2006). Pollock (1999) reported PTSD occurring in 52% of the 80 investigated perpetrators who were accused of committing homicide. Probability for developing PTSD depended on the offender's personality traits and the form of violence chosen. Evans et al. (2007a,b) found in a sample of 105 offenders, who had been convicted of killing or seriously harming someone that 46% suffered from intrusive memories and 6% from PTSD. The authors assume that factors predicting reexperiencing symptoms like flashbacks in victims could be generalized to culprits. The probability of developing PTSD is also influenced by the impulsivity of a crime. Reactive homicide for example refers to a spontaneous and emotional driven aggression and yields a high risk of evolving negative feelings which may lead to PTSD. Instrumental homicide in contrast is goal-directed, planned, and proactive. There is no actual provocation required and the victim can be completely meaningless to the culprit (Christianson et al., 2007). On the other hand, not only unrequested memories like in PTSD can plague offenders, dissociative amnesia for the offense can occur as well. In a population of 207 convicts sentenced to life imprisonment, Pyszora et al. (2003) found amnesia primarily to be connected to preceding alcohol abuse, blackouts, psychiatric disorders, and crimes of passion. Among the 105 perpetrators studied by Evans et al. (2009a), 19% stated to have partial amnesia and 1% complete amnesia for their offense (cf. Parwatikar, 1990). The type of crime also affects the probability of developing amnesia. Reactive violent offends lead to memory loss more often than instrumental violent crimes (Cooper and Yuille, 2007).

Investigators do not only have to face several memory distortion phenomena while working with delinquents. They also have to calculate the risk of deceitful tendencies like denying or malingering. For a perpetrator, deceiving about what he or she did or at least feigning a memory impairment can be appealing in terms of some legal implications, like criminal responsibility and competency to stand trial (Porter et al., 2001). A culprit who cannot remember the details of his or her crime can hardly make an expedient contribution to his defense. Expert advice is needed in those cases to proof if the memory impairment is caused by organic disease, dissociative amnesia, a psychotic episode, or feigned amnesia (Bourget and Whitehurst, 2007), though a differentiation between dissociative (also called "psychogenic") amnesia and amnesia with organic origin is questionable (Barbarotto et al., 1996). Markowitsch and colleagues (Markowitsch et al., 1997, 2000a; Markowitsch, 1999) reported deviated brain activity measured by PET and SPECT in several patients with dissociative amnesia diagnosis. Feigned amnesia is not only problematic because it has to be detected in the first place. It can also impair memory performance. After a mock crime, van Oorsouw and Merckelbach (2004) instructed a group of participants to feign amnesia in a free recall test. A week later, participants completed the free recall test again but were briefed to respond honestly. Their performance was compared to the results of two control groups: one group made honest efforts on both tests, the immediate and the delayed, the other group only attended on the delayed test. The group that had been honest all the time and took part in both trials outperformed the simulators and the controls that underwent the test for the first time. The authors suggest that malingering might have similar effects as a lack of rehearsal. Analogous results have been observed in other studies (Christianson and Bylin, 1999; van Oorsouw and Merckelbach, 2006).

This may also be very important in the light of offenders' often claimed wish to forget about their crime. Next to a lack of rehearsal, several other reasons must be considered to possibly evoke amnesia (Christianson et al., 2007). For example, the differences between the highly emotional and arousing state during the act of crime and the calm environment of the criminal investigation could hinder correct retrospection, whereas recreating the context and the internal state during the crime could facilitate memorization (cf. the state-dependency of memory; Markowitsch and Staniloiu, 2012). Other conceivable explanations are intoxication, head injuries, brain diseases, or failures in meta-memory, i.e., for example the own conviction of being amnesic.

Several attempts have been made to detect lying using brain imaging technology, like in the above-mentioned study by Bhatt et al. (2009). And in pathological liars, white matter seems to be reduced in prefrontal regions (Yang et al., 2005). Markowitsch et al. (2000b) compared brain activation corresponding to real and fictitious autobiographical events and found the original events to evoke a neural response in the right amygdala, the right temporofrontal junction areas, and other cortical regions, while the invented stories led to activation in the precuneus. The differences may be caused by the stories' unequal emotional attraction and the precuneus' well-known role in mental imagery.

The question arises, whether neural correlates of delinquent behavior exist. Some evidence has been found concerning brain

structure and brain activity alteration in individuals with criminal background or antisocial personality disorder. Differences can be observed, e.g., in the frontal lobes, in frontotemporal regions, and in limbic structures (Bassarath, 2001). But caution is indicated, since some of these changes can be found in persons not perpetrating crimes as well, and so in this context, no exclusive relationship between brain and behavior anomalies has been proofed to date (Markowitsch and Kalbe, 2007).

These findings illustrate that offenders' memory abilities might differ in many ways from eyewitnesses' capacities for remembering. The differences may be due to the perpetrators specific involvement in the act of crime, comorbidities like intoxication, PTSD, amnesia, or antisocial personality disorder or intended forgetting. A divergence in face processing is accompanied by a change in brain function and may also modulate emerging memory tracks for face stimuli even under normal conditions. Finally, the questionable truthfulness of the investigated persons exacerbates the researcher's effort of shedding some light into culprits' powers of recollection.

REALITY VS. LABORATORY

Science has already made a wide range of contributions to legal implications concerning the treatment of eyewitnesses in recent years, like the cognitive interview (Holliday et al., 2012; Sharman and Powell, 2013) or several approaches of evolving facial composites (Frowd et al., 2012a,b). But in reforming the existing procedures, we have to weigh costs against benefits (Clark, 2012). In many cases, a reduction of false identifications is accompanied by a reduction in correct identifications as well. Further investigation is needed, and with the advent of neuroimaging techniques, research also starts to unravel the underlying neural mechanisms involved in person identification and face recognition. But these methods rely on laboratory settings and presumably lack ecological validity. While examining culprits, reliable data is even more difficult to obtain, as an offender's cooperation without any intention of deceit cannot be taken for granted. Rightly the question arises whether results obtained under such laboratory conditions can be transferred to real felonious cases.

In the field of neuroimaging, original data of real-life events is obviously hard to come by. However, even if such precious pieces of data could be obtained, their interpretation would be more than challenging. Lacking the standardized methods used in experimental settings, performances of different eyewitnesses or offenders, perhaps even across different cases, would be rarely comparable. Nevertheless, the question arises whether laboratory studies can teach us something about the nature of eyewitness memory and what pitfalls might be waiting in their analysis.

A compromise is attempted in so-called ecologically valid testing situations. One such study was performed by Mohamed et al. (2006) who tested normal individuals under two opposing conditions. In one the subjects agreed to the statement that he or she fired a gun, and in the other they disagreed. In this way the same individual could be tested with functional brain imaging under both the lie and the truth condition. As expected from the results of subsequent studies (e.g., Markowitsch, 2008; Spence and Kaylor-Hughes, 2008; Markowitsch and Merkel, 2011), there was more activation during the lie than during the truth condition. Frontal, temporal, cingulate, fusiform, insular, and occipital areas were activated during the lie condition, while for the truth condition there was more limited frontal and temporal activation, possibly including the lenticular nucleus.

Ihlebæk et al. (2003) compared eyewitness memory originating from a video and a live condition. Subjects in the live condition took part in a staged bank or service station robbery. Robbers were performed by two police officers. For the video condition a recording was used which was made by one of the researchers. Their major finding was the difference between groups concerning the number of details reported, with participants in the video condition outmatching the other subjects. They reported more details and were more accurate. Nevertheless, the patterns of mistakes were quite similar, for example both groups over- or underestimated event duration and age of the robbers. As the authors point out, the lower rate of memorized details in the "live" group might be due to the fact that witnesses may have had less opportunity to watch the robbers closely, since some of them have been forced to get down to the floor and to cover their faces. This is supported by the fact that a high proportion of the differences between groups can be explained by "I don't know" answers. The authors outline that laboratory experiments may overestimate eyewitness memory, but that the kind of errors that are made are quite similar in both settings. It can be argued that a staged robbery still is an artificial event, in particular because the participants have been informed.

Wagstaff et al. (2003) conducted two studies to analyze archival testimonies of 70 and 48 real crime witnesses, respectively. In all cases the particular culprit was arrested and convicted. They tried to discover, how the level of violence, the presence of a weapon, and the age of witnesses affect memory accuracy regarding the offender's age, height, build, hair color, and hairstyle. Violence (and also partly the type of crime) predicted memory performance concerning hair color; the higher the level of violence, the more accurate the victims' judgments regarding this aspect. Witnesses to rape also gave more precise statements concerning hair color than witnesses to robbery. But both factors, violence and type of crime, were not unrelated, since crimes of rape involved higher rates of violence in the investigated cases. Closer distance to the culprit, a longer exposure time (Memon et al., 2003b), or the higher probability of knowing the offender are conceivable explanations which might have contributed to these results.

We have performed two experiments in which we tested eyewitnesses under laboratory conditions. In the first study (Kühnel et al., 2008), normal participants studied short movies (each of less than 4 min duration). Thereafter they had to respond with YES (seen) or NO (not seen) to individual pictures which either stemmed from the movie or not. Some of these single shots had a high likeliness of having been in the respective movie and some not. Overall, participants made almost 45% erroneous responses. However, brain images obtained with functional magnetic resonance imaging (fMRI) revealed a more clear-cut picture: the correctly identified pictures led to a medial prefrontal/anterior cingulate activation while the falsely identified resulted in activations in the visual association cortex and the precuneus (all bilaterally) (**Figure 1**). In a second study (Risius et al., 2013) we again used a film and asked normal participants later during fMRI

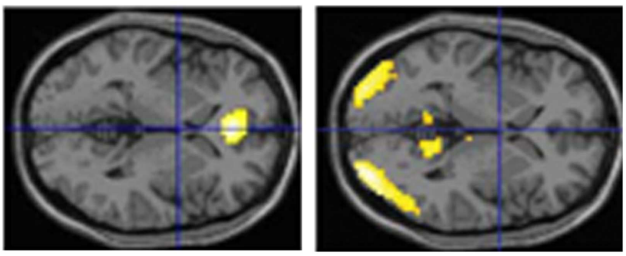


FIGURE 1 | Brain imaging activations during correct or false identification of visual stimuli in the study of Kühnel et al. (2008) (horizontal sections; left: activations during correct answers, right: activation during false answers).

to judge whether a statement referring to the film was correct or not. Furthermore, they had to give confidence judgments for each choice and – if they wished – they could bet that their answer was correct. If this happened, activations were found in temporal, frontal, and middle and posterior cingulate areas as well as in the precuneus. Otherwise cingulate and medial temporal regions were activated. Withholding an answer (as compared to volunteering it) resulted in increased bilateral hippocampal activations as well as in an activation in the left caudate nucleus.

Several factors may influence eyewitness memory and especially by the use of field studies it is difficult to discover which of them are crucial and how they might interact with each other. Laboratory experiments can manipulate single factors and give us an idea of the underlying processes, restricted to the fact that experimental designs differ in many characteristics from real criminal experiences. But even those authentic events differ in many aspects such as stress-level, amount of violence, weapon presence, distance to the offender, and if he or she is familiar to the eyewitness. Many attempts have to be made to complete this mosaic. Therefore Chae (2010, p. 259) concluded: "No single study, either naturalistic or experimental, can cover all the relevant factors present in forensic situations." With regards to the benefit of field tests of eyewitness identification procedures Schacter et al. (2008, p. 5) recommended: "No single field study can produce a final blueprint for procedural reform; we will need many." And so both approaches – field and laboratory research – bring their advantages into account: ecological validity and experimental control. But a lot of effort has to be made to compensate for their disadvantages and to integrate the findings into a coherent picture.

CONCLUSION AND OUTLOOK

The multitude of parameters affecting eyewitness' and offender's memories illustrates the need for standardized methods regarding the treatment of witnesses and suspects. But not only police officers have to be sensitized for the influences their interview techniques might have on the reliability of testimonies and how best recollection results can be obtained. Also judges, advocates, and jurors must be informed about the differences between procedures, the impact they have on memory quality and other factors working in favor of memory distortion. It is science's responsibility not only to evolve, develop, and test those methods in cooperation with operators, but to educate judging persons how results have to be interpreted and how much value should be attached to them (Markowitsch and Merkel, 2011; Markowitsch and Staniloiu, 2011; Schacter and Loftus, 2013).

This is also true for the upcoming neuroimaging techniques like fMRI. The investigation of brain function in criminal contexts is a young field of research. The prospect of detecting false memories in eyewitnesses and deception in offenders is highly appealing. Although, achievement of these objectives would render a great service, it is still quite a long way before this technique is able to clarify ongoing brain processes in a reliable manner. Neuroimaging data is hard to interpret; all the more because we lack ecologically valid studies. Face processing for example is modulated by facial characteristics and how familiar the shown person is to us, but our feelings for this person will affect our brain activity as well. It does make a difference if we watch a beloved or a neutral person's face or if we look at someone we might fear or be angry about. Encouraging are the results of Lefebvre et al. (2007) who found the event-related brain potential P300 to indicate correct target identification in a lineup task. Nevertheless, it still has to be explored to what extent these findings can be transferred to other criminal contexts.

Investigation of perpetrators' memory is even more demanding, since results are often confounded by different comorbidities, like intoxication or personality disorders. Those concomitant phenomena can cause alternated face processing even under normal conditions. If we want to learn about offenders' brain functions, we must examine those processes in different settings and untangle the confounding factors, but we also must control for deceitful tendencies culprits might have.

Accordingly, we have to meet the challenge of taming the technical demands on the one side and to discriminate the neural activity associated with a special mental state on the other. We still have to learn a lot about brain function in the context of criminal events to know what we are searching for in an eyewitness' or offender's head. Even if we could rely on authentic data, fMRI technique still has to be improved. Up to now it is not possible to reliably detect false memory or deception by brain imaging outside the laboratory. Laymen might believe in data obtained by brain scans as objective proof of ongoing brain function, but it has to be pointed out that it is a product of many decisions made by the researcher, like the extent of the statistical power, conformation of individual brain structure to a standardized anatomical brain model, and other fine adjustments and corrections (Bumann, 2010). Furthermore, it is dangerous to draw conclusions from group analysis to single subjects. Group data are achieved by averaging data across individuals. In the extreme, it is possible that no single subject exhibits an activation pattern as the average mean suggests. Another risk consists in making a wrong deduction by "reverse inference" (Poldrack, 2006), that is to infer the presence of a special mental state or function on the finding of a special brain activation pattern. If such a pattern of activity is found, we cannot be sure that a special mental state, which also has been observed to show this pattern, is indeed present, since brain structures normally fulfill many different tasks. On the other hand, the absence of a pattern, correlated to a special mental state in group analysis, does not mean that the state of interest must be absent as well, as

other brain areas could execute the respective cognitive function. Nevertheless, the potential of these techniques is enormous, and there is a lot to learn on the way. Therefore, it is important not to lose courage, to make the attempt to unravel the underlying processes, and to obtain data from real cases.

REFERENCES

Adolphs, R., Tranel, D., and Damasio, A. R. (1998). The human amygdala in social judgment. *Nature* 393, 470–474. doi:10.1038/30982

Andreano, J. M., and Cahill, L. (2006). Glucocorticoid release and memory consolidation in men and women. *Psychol. Sci.* 17, 466–470. doi:10.1111/j.1467-9280.2006.01729.x

Barbarotto, R., Laiacona, M., and Cocchini, G. (1996). A case of simulated, psychogenic or focal pure retrograde amnesia: did an entire life become unconscious? *Neuropsychologia* 34, 575–585. doi:10.1016/0028-3932(95)00141-7

Bassarath, L. (2001). Neuroimaging studies of antisocial behaviour. *Can. J. Psychiatry* 46, 728–732.

Behrman, B. W., and Davey, S. L. (2001). Eyewitness identification in actual criminal cases: an archival analysis. *Law Hum. Behav.* 25, 475–491. doi:10.1023/A:1012840831846

Bhatt, S., Mbwana, J., Adeyemo, A., Sawyer, A., Hailu, A., and VanMeter, J. (2009). Lying about facial recognition: an fMRI study. *Brain Cogn.* 69, 382–390. doi:10.1016/j.bandc.2008.08.033

Bisby, J. A., Leitz, J. R., Morgan, C. J. A., and Curran, H. V. (2010). Decreases in recollective experience following acute alcohol: a dose-response study. *Psychopharmacology (Berl.)* 208, 67–74. doi:10.1007/s00213-009-1709-y

Bourget, D., and Whitehurst, L. (2007). Amnesia and crime. *J. Am. Acad. Psychiatry Law* 35, 469–480.

Brainerd, C. J., and Reyna, V. F. (2005). *The Science of False Memory*. New York: Oxford University Press.

Bumann, B. (2010). The future of neuroimaging in witness testimony. *Virtual Mentor* 12, 873–878. doi:10.1001/virtualmentor.2010.12.11.hlaw1-1011

Busey, T. A., and Loftus, G. R. (2007). Cognitive science and the law. *Trends Cogn. Sci.* 11, 111–117. doi:10.1016/j.tics.2006.12.004

Cahill, L., Gorski, L., and Le, K. (2003). Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. *Learn. Mem.* 10, 270–274. doi:10.1101/lm.62403

Camp, G., Wesstein, H., and de Bruin, A. B. H. (2012). Can questioning induce forgetting? Retrieval-induced forgetting of eyewitness information. *Appl. Cogn. Psychol.* 26, 431–435. doi:10.1002/acp.2815

Chae, Y. (2010). Application of laboratory research on eyewitness testimony. *J. Forensic Psychol. Pract.* 10, 252–261. doi:10.1080/15228930903550608

Christianson, S.-A., and Bylin, S. (1999). Does simulating amnesia mediate genuine forgetting for a crime event? *Appl. Cogn. Psychol.* 13, 495–511. doi:10.1002/(SICI)1099-0720(199912)13:6<495::AID-ACP615>3.0.CO;2-0

Christianson, S. A., Freij, I., and von Vogelsang, E. (2007). "Searching for offenders memories of violent crimes," in *Offenders Memories of Violent Crimes*, ed. S. A. Christianson (West Sussex: Wiley), 3–35.

Clark, S. E. (2012). Costs and benefits of eyewitness identification reform: psychological science and public policy. *Perspect. Psychol. Sci.* 7, 238–259. doi:10.1177/1745691612439584

Clark, S. E., and Tunnicliff, J. L. (2001). Selecting lineup foils in eyewitness identification experiments: experimental control and real-world simulation. *Law Hum. Behav.* 25, 199–216. doi:10.1023/A:1010753809988

Clifford, B. R., Havard, C., Memon, A., and Gabbert, F. (2012). Delay and age effects on identification accuracy and confidence: an investigation using a video identification parade. *Appl. Cogn. Psychol.* 26, 130–139. doi:10.1002/acp.1804

Connors, E., Lundregan, T., Miller, N., and McEwen, T. (1996). *Convicted by Juries, Exonerated by Science: Case Studies in the Use of DNA Evidence to Establish Innocence After Trial*. Alexandria, VA: National Institute of Justice.

Cooper, B. S., and Yuille, J. C. (2007). "An investigation of violent offenders memories for instrumental and reactive violence," in *Offenders Memories of Violent Crimes*, ed. S. A. Christianson (West Sussex: Wiley), 75–97.

Damasio, A. R., Tranel, D., and Damasio, H. (1990). Face agnosia and the neural substrates of memory. *Annu. Rev. Neurosci.* 13, 89–109. doi:10.1146/annurev.ne.13.030190.000513

de Quervain, D. J.-F., Aerni, A., and Roozendaal, B. (2007). Preventive effect of β-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. *Am. J. Psychiatry* 164, 967–969. doi:10.1176/appi.ajp.164.6.967

Demos, K. E., Kelley, W. M., Ryan, S. L., Davis, F. C., and Whalen, P. J. (2008). Human amygdala sensitivity to the pupil size of others. *Cereb. Cortex* 18, 2729–2734. doi:10.1093/cercor/bhn034

Dysart, J. E., Lindsay, R. C. L., MacDonald, T. K., and Wicke, C. (2002). The intoxicated witness: effects of alcohol on identification accuracy from showups. *J. Appl. Psychol.* 87, 170–175. doi:10.1037/0021-9010.87.1.170

Easterbrook, J. A. (1959). The effect of emotion on cue utilization and the organization of behavior. *Psychol. Rev.* 66, 183–201. doi:10.1037/h0047707

Echterhoff, G., and Wolf, O. T. (2012). The stressed eyewitness: the interaction of thematic arousal and post-event stress in memory for central and peripheral event information. *Front. Integr. Neurosci.* 6:57. doi:10.3389/fnint.2012.00057

Eich, J. E. (1980). The cue-dependent nature of state-dependent retrieval. *Mem. Cognit.* 8, 157–173. doi:10.3758/BF03213419

Elgar, K., and Campbell, R. (2001). Annotation: the cognitive neuroscience of face recognition: implications for developmental disorders. *J. Child Psychol. Psychiatry* 42, 705–717. doi:10.1111/1469-7610.00767

Evans, C. (2006). What violent offenders remember of their crime: empirical explorations. *Aust. N. Z. J. Psychiatry* 40, 508–518. doi:10.1111/j.1440-1614.2006.01833.x

Evans, C., Ehlers, A., Mezey, G., and Clark, D. M. (2007a). Intrusive memories in perpetrators of violent crime: emotions and cognitions. *J. Consult. Clin. Psychol.* 75, 134–144. doi:10.1037/0022-006X.75.1.134

Evans, C., Ehlers, A., Mezey, G., and Clark, D. M. (2007b). Intrusive memories and ruminations related to violent crime among young offenders: phenomenological characteristics. *J. Trauma Stress* 20, 183–196. doi:10.1002/jts.20204

Evans, C., Mezey, G., and Ehlers, A. (2009a). Amnesia for violent crime among young offenders. *J. Forens. Psychiatry Psychol.* 20, 85–106. doi:10.1080/14789940802234471

Evans, J. R., Schreiber Compo, N., and Russano, M. B. (2009b). Intoxicated witnesses and suspects: procedures and prevalence according to law enforcement. *Psychol. Public Policy Law* 15, 194–221. doi:10.1037/a0016837

Evans, J. R., and Schreiber Compo, N. (2010). Mock jurors' perceptions of identifications made by intoxicated eyewitnesses. *Psychol. Crime Law* 16, 191–210. doi:10.1080/10683160802612890

Firestone, A., Turk-Browne, N. B., and Ryan, J. D. (2007). Age-related deficits in face recognition are related to underlying changes in scanning behavior. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 14, 594–607. doi:10.1080/13825580600899717

Fitzgerald, D. A., Arnold, J. F., Becker, E. S., Speckens, A. E. M., Rinck, M., Rijpkema, M., et al. (2011). How mood challenges emotional memory formation: an fMRI investigation. *Neuroimage* 56, 1783–1790. doi:10.1016/j.neuroimage.2011.02.061

Frowd, C. D., Nelson, L., Skelton, F., Noyce, R., Atkins, R., Heard, P., et al. (2012a). Interviewing techniques for Darwinian facial-composite systems. *Appl. Cogn. Psychol.* 26, 576–584. doi:10.1002/acp.2829

Frowd, C. D., Pitchford, M., Skelton, F., Petkovic, A., Prosser, C., and Coates, B. (2012b). "Catching even more offenders with EvoFIT facial composites," in *Third International Conference on Emerging Security Technologies (EST)* (Washington DC: IEEE Computer Society Washington), 20–26. doi:10.1109/EST.2012.26

Frowd, C. D., Skelton, F., Atherton, C., Pitchford, M., Hepton, G., Holden, L., et al. (2012c). Recovering faces from memory: the distracting influence of external facial features. *J. Exp. Psychol.* 18, 224–238. doi:10.1037/a0027393

García-Bajos, E., Migueles, M., and Aizpurua, A. (2012). Bias of script-driven processing on eyewitness memory in young and older adults. *Appl. Cogn. Psychol.* 26, 737–745. doi:10.1002/acp.2854

Gobbini, M. I., and Haxby, J. V. (2006). Neural response to the visual familiarity of faces. *Brain Res. Bull.* 71, 76–82. doi:10.1016/j.brainresbull.2006.08.003

Gobbini, M. I., and Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia* 45, 32–41. doi:10.1016/j.neuropsychologia.2006.04.015

Gobbini, M. I., Leibenluft, E., Santiago, N., and Haxby, J. V. (2004). Social and emotional attachment in the neural representation of faces. *Neuroimage* 22, 1628–1635. doi:10.1016/j.neuroimage.2004.03.049

Godden, D. R., and Baddeley, A. D. (1975). Context-dependent memory in two natural environments: on land and underwater. *Br. J. Psychol.* 66, 325–331. doi:10.1111/j.2044-8295.1975.tb01468.x

Golby, A. J., Gabrieli, J. D. E., Chiao, J. Y., and Eberhardt, J. L. (2001). Differential responses in the fusiform region to same-race and other-race faces. *Nat. Neurosci.* 4, 845–850. doi:10.1038/90565

Goodwin, D. W., Powell, B., Bremer, D., Hoine, H., and Stern, J. (1969). Alcohol and recall: state-dependent effects in man. *Science* 163, 1358–1360. doi:10.1126/science.163.3873.1358

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., and Malach, R. (2004). Intersubject synchronization of cortical activity during natural vision. *Science* 303, 1634–1640. doi:10.1126/science.1089506

Henke, K., Landis, T., and Markowitsch, H. J. (1994). Subliminal perception of words and faces. *Int. J. Neurosci.* 75, 181–187. doi:10.3109/00207459408986302

Hoff, H., Beneventi, H., Galta, K., and Wik, G. (2009). Evidence of deviant emotional processing in psychopathy: a fMRI case study. *Int. J. Neurosci.* 119, 857–878. doi:10.1080/00207450701590992

Hoffman, R. E., Esposito, R., Rosen, M., and Rockholz, P. (1997). Recurrent personal memories during intoxication reported by patients with alcoholism. *Psychol. Med.* 27, 1441–1446. doi:10.1017/S0033291797005400

Hofmann, S. G., Suvak, M., and Litz, B. T. (2006). Sex differences in face recognition and influence of facial affect. *Pers. Indiv. Diff.* 40, 1683–1690. doi:10.1016/j.paid.2005.12.014

Holliday, R. E., Humphries, J. E., Milne, R., Memon, A., Houlder, L., Lyons, A., et al. (2012). Reducing misinformation effects in older adults with cognitive interview mnemonics. *Psychol. Aging* 27, 1191–1203. doi:10.1037/a0022031

Hope, L., Lewinski, W., Dixon, J., Blocksidge, D., and Gabbert, F. (2012). Witnesses in action: the effect of physical exertion on recall and recognition. *Psychol. Sci.* 23, 386–390. doi:10.1177/0956797611431463

Humphries, J. E., Holliday, R. E., and Flowe, H. D. (2012). Faces in motion: age-related changes in eyewitness identification performance in simultaneous, sequential and elimination video lineups. *Appl. Cogn. Psychol.* 26, 149–158. doi:10.1002/acp.1808

Hurlemann, R. (2006). Noradrenergic control of emotion-induced amnesia and hypermnesia. *Rev. Neurosci.* 17, 525–532. doi:10.1515/REVNEURO.2006.17.5.525

Hurlemann, R., Hawellek, B., Matusch, A., Kolsch, H., Wollersen, H., Madea, B., et al. (2005). Noradrenergic modulation of emotion-induced forgetting and remembering. *J. Neurosci.* 25, 6343–6349. doi:10.1523/JNEUROSCI.0228-05.2005

Ihlebæk, C., Løve, T., Eilertsen, D. E., and Magnussen, S. (2003). Memory for a staged criminal event witnessed live and on video. *Memory* 11, 319–327. doi:10.1080/09658210244000018

Iiadaka, T., Harada, T., Kawaguchi, J., and Sadato, N. (2012). Neuroanatomical substrates involved in true and false memories for face. *Neuroimage* 62, 167–176. doi:10.1016/j.neuroimage.2012.04.044

Itier, R. J., Latinus, M., and Taylor, M. J. (2006). Face, eye and object early processing: what is the face specificity? *Neuroimage* 29, 667–676. doi:10.1016/j.neuroimage.2005.07.041

Johnson, K. J., and Frederickson, B. L. (2005). "We all look the same to me": positive emotions eliminate the own-race bias in face recognition. *Psychol. Sci.* 16, 875–881. doi:10.1111/j.1467-9280.2005.01631.x

Jones, A. P., Laurens, K. R., Herba, C. M., Barker, G. J., and Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *Am. J. Psychiatry* 166, 95–102. doi:10.1176/appi.ajp.2008.07071050

Kassin, S. M., Tubb, V. A., Hosch, H. M., and Memon, A. (2001). On the "general acceptance" of eyewitness testimony research – a new survey of the experts. *Am. Psychol.* 56, 405–416. doi:10.1037/0003-066X.56.5.405

Kaufmann, J. M., and Schweinberger, S. R. (2004). Expression influences the recognition of familiar faces. *Perception* 33, 399–408. doi:10.1068/p5083

Kensinger, E. A., Garoff-Eaton, R. J., and Schacter, D. L. (2006). Memory for specific visual details can be enhanced by negative arousing content. *J. Mem. Lang.* 54, 99–112. doi:10.1016/j.jml.2005.05.005

Kensinger, E. A., Garoff-Eaton, R. J., and Schacter, D. L. (2007). Effects of emotion on memory specificity: memory trade-offs elicited by negative visually arousing stimuli. *J. Mem. Lang.* 56, 575–591. doi:10.1016/j.jml.2006.05.004

Kensinger, E. A., and Schacter, D. L. (2007). Effects of aging and encoding instructions on emotion-induced memory trade-offs. *Psychol. Aging* 22, 781–795. doi:10.1037/0882-7974.22.4.781

Kuhlmann, S., Piel, M., and Wolf, O. T. (2005). Impaired memory retrieval after psychosocial stress in healthy young men. *J. Neurosci.* 25, 2977–2982. doi:10.1523/JNEUROSCI.5139-04.2005

Kuhlmann, S., and Wolf, O. T. (2006). Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behav. Neurosci.* 120, 217–223. doi:10.1037/0735-7044.120.1.217

Kühnel, S., and Markowitsch, H. J. (2009). *Falsche Erinnerungen.* Heidelberg: Spektrum.

Kühnel, S., Woermann, F. G., Mertens, M., and Markowitsch, H. J. (2008). Involvement of the orbitofrontal cortex during correct and false recognitions of visual stimuli. Implications for eyewitness decisions on an fMRI study using a film paradigm. *Brain Imag. Behav.* 2, 163–176. doi:10.1007/s11682-008-9026-3

Lander, K., and Davies, R. (2007). Exploring the role of characteristic motion when learning new faces. *Q. J. Exp. Psychol.* 60, 519–526. doi:10.1080/17470210601117559

Lee, Y., Anaki, D., Grady, C. L., and Moscovitch, M. (2012). Neural correlates of temporal integration in face recognition: an fMRI study. *Neuroimage* 61, 1287–1299. doi:10.1016/j.neuroimage.2012.02.073

Lefebvre, C. D., Marchand, Y., Smith, S. M., and Connolly, J. F. (2007). Determining eyewitness identification accuracy using event-related brain potentials (ERPs). *Psychophysiology* 44, 894–904. doi:10.1111/j.1469-8986.2007.00566.x

Lewin, C., and Herlitz, A. (2002). Sex differences in face recognition – women's faces make the difference. *Brain Cogn.* 50, 121–128. doi:10.1016/S0278-2626(02)00016-7

Liu, D. L. J., Graham, S., and Zorawski, M. (2008). Enhanced selective memory consolidation following post-learning pleasant and aversive arousal. *Neurobiol. Learn. Mem.* 89, 36–46. doi:10.1016/j.nlm.2007.09.001

Loftus, E. F. (2011). Intelligence gathering post-9/11. *Am. Psychol.* 66, 532–541. doi:10.1037/a0024614

Markowitsch, H. J. (1999). Functional neuroimaging correlates of functional amnesia. *Memory* 7, 561–583. doi:10.1080/096582199387751

Markowitsch, H. J. (2008). Neuroscience and crime. *Neurocase* 14, 1–6. doi:10.1080/13554790801994756

Markowitsch, H. J., and Kalbe, E. (2007). "Neuroimaging and Crime," in *Offenders Memories of Violent Crimes*, ed. S. A. Christianson (West Sussex: Wiley), 137–164.

Markowitsch, H. J., Kessler, J., van der Ven, C., Weber-Luxenburger, G., Albers, M., and Heiss, W. D. (1997). Psychic trauma causing grossly reduces brain metabolism and cognitive deterioration. *Neuropsychologia* 36, 77–82. doi:10.1016/S0028-3932(97)00093-6

Markowitsch, H. J., Kessler, J., Weber-Luxenburger, G., van der Ven, C., Albers, M., and Heiss, W. D. (2000a). Neuroimaging and behavioral correlates of recovery from mnestic block syndrome and other cognitive deteriorations. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 13, 60–66.

Markowitsch, H. J., Thiel, A., Reinkemeier, M., Kessler, J., Koyuncu, A., and Heiss, W.-D. (2000b). Right amygdalar and temporofrontol activation during autobiographic, but not during fictitious memory retrieval. *Behav. Neurol.* 12, 181–190.

Markowitsch, H. J., and Merkel, R. (2011). The brain stands trial. *Max-Planck Res.* 3, 12–17.

Markowitsch, H. J., and Staniloiu, A. (2011). Neuroscience and the law. *Cortex* 47, 1248–1251. doi:10.1016/j.cortex.2011.06.013

Markowitsch, H. J., and Staniloiu, S. (2012). Amnesic disorders. *Lancet* 380, 1229–1240. doi:10.1016/S0140-6736(11)61304-4

McBain, R., Norton, D., and Chen, Y. (2009). Females excel at basic face perception. *Acta Psychol.* 130, 168–173. doi:10.1016/j.actpsy.2008.12.005

McGaugh, J. L. (2013). Making lasting memories: remembering the significant. *Proc. Natl. Acad. Sci. U.S.A.* 110(Suppl. 2), 10402–10407. doi:10.1073/pnas.1301209110

McGaugh, J. L., and Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Curr. Opin. Neurobiol.* 12, 205–210. doi:10.1016/S0959-4388(02)00306-9

Megreya, A. M., and Bindemann, M. (2013). Individual differences in personality and face identification. *J. Cogn. Psychol.* 25, 30–37. doi:10.1080/20445911.2012.739153

Memon, A., Bartlett, J., Rose, R., and Gray, C. (2003a). The aging eyewitness: effects of age on face, delay, and source-memory ability. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 58B, 338–345. doi:10.1093/geronb/58.6.P338

Memon, A., Hope, L., and Bull, R. (2003b). Exposure duration: effects on eyewitness accuracy and confidence. *Br. J. Psychol.* 94, 339–354. doi:10.1348/000712603767876262

Migueles, M., and García-Bajos, E. (2007). Selective retrieval and induced forgetting in eyewitness memory. *Appl. Cogn. Psychol.* 21, 1157–1172. doi:10.1002/acp.1323

Mineka, S., and Oehlberg, K. (2008). The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta Psychol.* 127, 567–580. doi:10.1016/j.actpsy.2007.11.007

Minnebusch, D. A., Suchan, B., Köster, O., and Daum, I. (2009). A bilateral occipitotemporal network mediates face perception. *Behav. Brain Res.* 198, 179–185. doi:10.1016/j.bbr.2008.10.041

Mohamed, F. B., Faro, S. H., Gordon, N. J., Platek, S. M., Ahmad, H., and Williams, J. M. (2006). Brain mapping of deception and truth telling about an ecologically valid situation: functional MR imaging and polygraph investigation – initial experience. *Radiology* 238, 679–688. doi:10.1148/radiol.2382050237

Morgan, C. A. III, Southwick, S., Steffian, G., Hazlett, G. A., and Loftus, E. F. (2013). Misinformation can influence memory for recently experienced, highly stressful events. *Int. J. Law Psychiatry* 36, 11–17. doi:10.1016/j.ijlp.2012.11.002

Moulton, P. L., Petros, T. V., Apostal, K. J., Park, R. V., Ronning, E. A., King, B. M., et al. (2005). Alcohol-induced impairment and enhancement of memory: a test of the interference theory. *Physiol. Behav.* II, 240–245. doi:10.1016/j.physbeh.2005.03.011

Nasr, S., and Tootell, R. B. H. (2012). Role of fusiform and anterior temporal cortical areas in facial recognition. *Neuroimage* 63, 1743–1753. doi:10.1016/j.neuroimage.2012.08.031

Nestor, A., Plaut, D. C., and Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proc. Natl. Acad. Sci. U.S.A.* 108, 9998–10003. doi:10.1073/pnas.1102433108

Odegard, T. N., Cooper, C. M., Lampinen, J. M., Reyna, V. F., and Brainerd, C. J. (2009). Children's eyewitness memory for multiple real-life events. *Child Dev.* 80, 1877–1890. doi:10.1111/j.1467-8624.2009.01373.x

Oszoy, S., Durak, A. C., and Esel, E. (2013). Hippocampal volumes and cognitive functions in adult alcoholic patients with adolescent-onset. *Alcohol* 47, 9–14. doi:10.1016/j.alcohol.2012.09.002

O'Toole, A. J. (2005). "Psychological and neural perspectives on human face recognition," in *Handbook of Face Recognition*, eds S. Z. Li, and A. K. Jain (New York: Springer Science + Business Media), 349–369.

Palmer, F. T., Flowe, H. D., Takarangi, M. K. T., and Humphries, J. E. (2013). Intoxicated witnesses and suspects: an archival analysis of their involvement in criminal case processing. *Law Hum. Behav.* 37, 54–59. doi:10.1037/lhb0000010

Pardini, D. A., and Phillips, M. (2010). Neural responses to emotional and neutral facial expressions in chronically violent men. *J. Psychiatry Neurosci.* 35, 390–398. doi:10.1503/jpn.100037

Parvizi, J., Jacques, C., Foster, B. L., Withoft, N., Rangarajan, V., Weiner, K. S., et al. (2012). Electrical stimulation of human fusiform face-selective regions distorts face perception. *J. Neurosci.* 32, 14915–14920. doi:10.1523/JNEUROSCI.2609-12.2012

Parwatikar, S. D. (1990). "Medicolegal aspects of TGA," in *Transient Global Amnesia and Related Disorders*, ed. H. J. Markowitsch (Toronto: Hogrefe & Huber Publishing), 191–205.

Pfabigan, D. M., Alexopoulos, J., and Sailer, U. (2012). Exploring the effects of antisocial personality traits on brain potentials during face processing. *PLoS ONE* 7:e50283. doi:10.1371/journal.pone.0050283

Phelps, E. A., O'Connor, K. J., Cunningham, W. A., Funayama, E. S., Gatenby, J. C., Gore, J. C., et al. (2000). Performance on indirect measures of race evaluation predicts amygdale activation. *J. Cogn. Neurosci.* 12, 729–738. doi:10.1162/089892900562552

Poldrack, R. A. (2006). Can cognitive processes be inferred from neuroimaging data? *Trends Cogn. Sci.* 10, 59–63. doi:10.1016/j.tics.2005.12.004

Pollock, P. H. (1999). When the killer suffers: post-traumatic stress reactions following homicide. *Legal Criminol. Psychol.* 4, 185–202. doi:10.1348/135532599167842

Porter, S., Birt, A. R., Yuille, J. C., and Hervé, H. F. (2001). Memory for murder. A psychological perspective on dissociative amnesia in legal contexts. *Int. J. Law Psychiatry* 24, 23–42. doi:10.1016/S0160-2527(00)00066-2

Pyszora, N. M., Barker, A. F., and Kopelman, M. D. (2003). Amnesia for criminal offences: a study of life sentence prisoners. *J. Forens. Psychiatry Psychol.* 14, 475–490. doi:10.1080/14789940310001599785

Qin, S., Hermans, E. J., van Merle, H. J. F., and Fernández, G. (2012). Understanding low reliability of memories for neutral information encoded under stress: alterations in memory-related activation in the hippocampus and midbrain. *J. Neurosci.* 32, 4032–4041. doi:10.1523/JNEUROSCI.3101-11.2012

Rahman, Q., Wilson, G. D., and Abrahams, S. (2004). Sex, sexual orientation, and identification of positive and negative facial affect. *Brain Cogn.* 54, 179–185. doi:10.1016/j.bandc.2004.01.002

Ray, S., and Bates, M. E. (2006). Acute alcohol effects on repetition priming and word recognition memory with equivalent memory cues. *Brain Cogn.* 60, 118–127. doi:10.1016/j.bandc.2005.07.009

Read, J. D., Yuille, J. C., and Tollestrup, P. (1992). Recollections of a robbery – effects of arousal and alcohol upon recall and person identification. *Law Hum. Behav.* 16, 425–446. doi:10.1007/BF02352268

Rehnman, J., and Herlitz, A. (2007). Women remember more faces than man do. *Acta Psychol.* 124, 344–355. doi:10.1016/j.actpsy.2006.04.004

Risius, U.-M., Staniloiu, A., Piefke, M., Maderwald, S., Schulte, F., Brand, M., et al. (2013). Retrieval, monitoring and control processes: a 7 Tesla fMRI approach to memory accuracy. *Front. Behav. Neurosci.* 7:24. doi:10.3389/fnbeh.2013.00024

Roark, D. A., Barrett, S. E., Spence, M. J., Abdi, H., and O'Toole, A. J. (2003). Psychological and neural perspectives on the role of motion in face recognition. *Behav. Cogn. Neurosci. Rev.* 2, 15–46. doi:10.1177/1534582303002001002

Rossion, B., Hanseeuw, B., and Dricot, L. (2012). Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. *Brain Cogn.* 79, 138–157. doi:10.1016/j.bandc.2012.01.001

Sato, W., and Yoshikawa, S. (2013). Recognition memory for faces and scenes. *J. Gen. Psychol.* 140, 1–15. doi:10.1080/00221309.2012.710275

Schacter, D. L., Dawes, R., Jacoby, L. L., Kahneman, D., Lempert, R., Roediger, H. L., et al. (2008). Policy forum: studying eyewitness investigations in the field. *Law Hum. Behav.* 32, 3–5. doi:10.1007/s10979-007-9093-9

Schacter, D. L., and Loftus, E. F. (2013). Memory and law: what can cognitive neuroscience contribute? *Nat. Neurosci.* 16, 119–123. doi:10.1038/nn.3294

Schreiber Compo, N., Evans, J. R., Carol, R. N., Villalba, D., Ham, L. S., Garcia, T., et al. (2012). Intoxicated eyewitnesses: better than their reputation? *Law Hum. Behav.* 36, 77–86. doi:10.1037/h0093951

Schulte-Rüther, M., Markowitsch, H. J., Fink, G. R., and Piefke, M. (2007). Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *J. Cogn. Neurosci.* 19, 1354–1372. doi:10.1162/jocn.2007.19.8.1354

Schwabe, L., Böhringer, A., and Wolf, O. T. (2009). Stress disrupts context-dependent memory. *Learn. Mem.* 16, 110–113. doi:10.1101/lm.1257509

Schwabe, L., and Wolf, O. T. (2012). Stress modulates the engagement of multiple memory systems in classification learning. *J. Neurosci.* 32, 11042–11049. doi:10.1523/JNEUROSCI.1484-12.2012

Shah, N. J., Marshall, J. C., Zafiris, O., Schwab, A., Zilles, K., Markowitsch, H. J., et al. (2001). The neural correlates of person familiarity. A functional magnetic resonance imaging study with clinical implications. *Brain* 124, 804–815. doi:10.1093/brain/124.4.804

Sharman, S. J., and Powell, M. B. (2013). Do cognitive interview instructions contribute to false beliefs and memories? *J. Invest. Psychol. Offender Profil.* 10, 114–124. doi:10.1002/jip.1371

Smeets, T., Otgaar, H., Candel, I., and Wolf, O. T. (2008). True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. *Psychoneuroendocrinology* 33, 1378–1386. doi:10.1016/j.psyneuen.2008.07.009

Smeets, T., Wolf, O. T., Giesbrecht, T., Sijstermans, K., Telgen, S., and Joels, M. (2009). Stress selectively and lastingly promotes learning of context-related high arousing information. *Psychoneuroendocrinology* 34, 1152–1161. doi:10.1016/j.psyneuen.2009.03.001

Smith, S. M., and Vela, E. (2001). Environmental context-dependent memory: a review and meta-analysis. *Psychon. Bull. Rev.* 8, 203–220. doi:10.3758/BF03196157

Söderlund, H., Grady, C. L., Easdon, C., and Tulving, E. (2007). Acute effects of alcohol on neural correlates of episodic memory encoding. *Neuroimage* 35, 928–939. doi:10.1016/j.neuroimage.2006.12.024

Spence, S. A., and Kaylor-Hughes, C. J. (2008). Looking for truth and finding lies: the prospects for a nascent neuroimaging of deception. *Neurocase* 14, 68–81. doi:10.1080/13554790801992776

Steeves, J. K. E., Culham, J. C., Duchaine, B. C., Pratesi, C. C., Valyear, K. F., Schindler, I., et al. (2006). The fusiform face area is not sufficient for face recognition: evidence from a patient with dense prosopagnosia and no occipital face area. *Neuropsychologia* 44, 594–609. doi:10.1016/j.neuropsychologia.2005.06.013

Strange, B. A., Hurlemann, R., and Dolan, R. J. (2003). An emotion-induced retrograde amnesia in humans is amygdala- and β-adrenergic-dependent. *Proc. Natl. Acad. Sci. U.S.A.* 100, 13626–13631. doi:10.1073/pnas.1635116100

Strange, B. A., Kroes, M. C. W., Fan, J. E., and Dolan, R. J. (2010). Emotion causes targeted forgetting of established memories. *Front. Behav. Neurosci.* 4:175. doi:10.3389/fnbeh.2010.00175

Sugiura, M., Mano, Y., Sasaki, A., and Sadato, N. (2011). Beyond the memory mechanism: person-selective and nonselective processes in recognition of personally familiar faces. *J. Cogn. Neurosci.* 23, 699–715. doi:10.1162/jocn.2010.21469

Technical Working Group for Eyewitness Evidence. (2003). *Eyewitness Evidence: A Trainer's Manual for Law Enforcement*. Washington, DC: National Institute of Justice.

Tranel, D., Damasio, A. R., and Damasio, H. (1988). Intact recognition of facial expression, gender, and age in patients with impaired recognition of face identity. *Neurology* 38, 690–696. doi:10.1212/WNL.38.5.690

Turk, D. J., Handy, T. C., and Gazzaniga, M. S. (2005). Can perceptual expertise account for the own-race bias in face recognition? A split-brain study. *Cogn. Neuropsychol.* 22, 877–883. doi:10.1080/02643290442000383

Valentine, T., and Mesout, J. (2009). Eyewitness identification under stress in the London dungeon. *Appl. Cogn. Psychol.* 23, 151–161. doi:10.1002/acp.1463

van Oorsouw, K., and Merckelbach, H. (2004). Feigning amnesia undermines memory for a mock crime. *Appl. Cogn. Psychol.* 18, 505–518. doi:10.1002/acp.999

van Oorsouw, K., and Merckelbach, H. (2006). Simulating amnesia and memories of a mock crime. *Psychol. Crime Law* 12, 261–271. doi:10.1080/10683160500224477

van Oorsouw, K., and Merckelbach, H. (2012). The effects of alcohol on crime-related memories: a field study. *Appl. Cogn. Psychol.* 26, 82–90. doi:10.1002/acp.1799

Von Der Heide, R. J., Skipper, L. M., and Olson, I. R. (2013). Anterior temporal face patches: a meta-analysis and empirical study. *Front. Hum. Neurosci.* 7:17. doi:10.3389/fnhum.2013.00017

Wagstaff, G. F., MaCveigh, J., Boston, R., Scott, L., Brunas-Wagstaff, J., and Cole, J. (2003). Can laboratory findings on eyewitness testimony be generalized to the real world? An archival analysis of the influence of violence, weapon presence, and age on eyewitness accuracy. *J. Psychol.* 137, 17–28. doi:10.1080/00223980309600596

Waring, J. D., and Kensinger, E. A. (2009). Effects of emotional valence and arousal upon memory trade-offs with aging. *Psychol. Aging* 24, 412–422. doi:10.1037/a0015526

Weingartner, H., Adefris, W., Eich, J. E., and Murphy, D. L. (1976). Encoding–imagery specificity in alcohol state-dependent learning. *J. Exp. Psychol. Hum. Learn.* 2, 83–87. doi:10.1037/0278-7393.2.1.83

Wells, G. L., and Hasel, L. E. (2007). Facial composite production by eyewitnesses. *Curr. Dir. Psychol. Sci.* 16, 6–10. doi:10.1111/j.1467-8721.2007.00465.x

Wells, G. L., and Olson, E. A. (2003). Eyewitness testimony. *Annu. Rev. Psychol.* 54, 277–295. doi:10.1146/annurev.psych.54.101601.145028

West, R. L., and Stone, K. R. (2013). Age differences in eyewitness memory for a realistic event. *J. Gerontol. B Psychol. Sci. Soc. Sci.* doi:10.1093/geronb/gbt014

Winston, J. S., Strange, B. A., O'Doherty, J., and Dolan, R. J. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nat. Neurosci.* 5, 277–283. doi:10.1038/nn816

Wolf, O. T. (2012). Immediate recall influences the effects of pre-encoding stress on emotional episodic long-term memory consolidation in healthy young men. *Stress* 15, 272–280. doi:10.3109/10253890.2011.622012

Wolf, O. T., Kuhlmann, S., Buss, C., Hellhammer, D. H., and Kirschbaum, C. (2004). Cortisol and memory retrieval in humans – influence of emotional valence. *Ann. N. Y. Acad. Sci.* 1032, 195–197. doi:10.1196/annals.1314.019

Wright, D. B. (2007). The impact of eyewitness identifications from simultaneous and sequential lineups. *Memory* 15, 746–754. doi:10.1080/09658210701508401

Wright, D. B., and Sladden, B. (2003). An own gender bias and the importance of hair in face recognition. *Acta Psychol.* 114, 101–114. doi:10.1016/S0001-6918(03)00052-0

Yang, Y., Raine, A., Lencz, T., Bihrle, S., Lacasse, L., and Colletti, P. (2005). Prefrontal white matter in pathological liars. *Br. J. Psychiatry* 187, 320–325. doi:10.1192/bjp.187.4.320

Yarmey, A. D. (2004). Eyewitness recall and photo identification: a field experiment. *Psychol. Crime Law* 10, 53–68. doi:10.1080/1068316021000058379

Yoon, H. W., Chung, J.-Y., Oh, J.-H., Min, H.-K., Kim, D.-J., Cheon, Y., et al. (2009). Differential activation of face memory encoding tasks in alcohol-dependent patients compared to healthy subjects: an fMRI study. *Neurosci. Lett.* 450, 311–316. doi:10.1016/j.neulet.2008.12.011

Yuille, J. C., and Tollestrup, P. A. (1990). Some effects of alcohol on eyewitness memory. *J. Appl. Psychol.* 75, 268–273. doi:10.1037/0021-9010.75.3.268

Zhu, B., Chen, C. S., Loftus, E. F., Lin, C. D., He, Q. H., Chen, C. H., et al. (2010). Individual differences in false memory from misinformation: cognitive factors. *Memory* 18, 543–555. doi:10.1080/09658211.2010.487051

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Using voxel-based morphometry to examine the relationship between regional brain volumes and memory performance in amnestic mild cognitive impairment

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Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder, in which morphological alterations of brain tissue develop many years before the first neuropsychological and clinical changes occur. Among the first and most prominent symptoms are deficiencies of declarative memory functions. This stage of precursory symptoms to AD has been described as amnestic mild cognitive impairment (aMCI) and is discussed as a potential AD prodrome. As therapy in the later stages of AD has been shown to be of limited impact, aMCI would be the key target for early intervention. For that purpose a comprehensive neuropsychological and anatomical characterization of this group is necessary. Previous neuropsychological investigations identified tests which are highly sensitive in diagnosing aMCI and very early AD. However, the sensitivity of those neuropsychological tests to the particular structural neuropathology in aMCI remains to be specified. To this end, we investigated 25 patients with single-domain aMCI. All participants underwent extensive neuropsychological testing and anatomical scanning with structural magnetic resonance imaging. Voxel-based morphometry (VBM) was performed to identify brain regions that show a significant correlation between regional brain volume and behavioral measures of memory and executive functioning. We found that performance in a variety of mnemonic tests was directly related to the integrity of the medial temporal lobe cortex (MTLC). Moreover, impairment of memory sub-functions in aMCI might be detected earlier than overt structural damage. By this, these findings contribute to the identification of cerebral structures associated with memory deficits in aMCI.

Keywords: voxel-based morphometry, amnestic mild cognitive impairment, neuropsychological tests, medial temporal lobe, episodic memory, semantic memory

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition, in which neuropathological changes of brain tissue advance many years before the first clinically detectable neuropsychological alterations occur. The transitional phase in which first neuropsychological performance deficits become subjectively – and objectively – detectable but are not severe enough to be diagnosed as dementia has been labeled as mild cognitive impairment (MCI). Depending on the involvement of only one or of several cognitive domains (single-domain vs. multiple-domain MCI) and if one of the compromised functions is memory (amnestic vs. non-amnestic MCI), there are four possible subtypes of MCI (Petersen, 2004). As shown by the results of longitudinal studies, particularly the single-domain amnestic MCI (aMCI) subtype is related to an increased probability of converting to dementia whereby AD was the most prevalent demential outcome (Busse et al., 2006; Yaffe et al., 2006; Fischer et al., 2007). Hence, aMCI is rather considered to constitute a precursory phase of AD than the other subtypes. This makes a deeper investigation and understanding of aMCI-related memory impairments and their structural neural correlates a significant purpose for an early diagnosis of AD.

In the course of AD, neurofibrillary pathology, in the form of tangles made up of hyperphosphorylated tau, begins in the perirhinal cortex, and then spreads to the entorhinal cortex and the hippocampus proper (Braak and Braak, 1991). This observation is in agreement with numerous imaging studies that have found medial temporal lobe (MTL) atrophy in early AD as well as in aMCI (Pennanen et al., 2004).

Moreover, various studies have investigated the volume of the MTL with structural MRI scans in AD and MCI (aMCI or across subtypes) using manual tracing methods or voxel-based morphometry (VBM). AD patients showed significant neuronal atrophy in the MTL including the hippocampus (e.g., Karas et al., 2004; Barbeau et al., 2008; Pihlajamäki et al., 2009; Schmidt-Wilcke et al., 2009) whereas patients with MCI only displayed major neuronal

loss in the medial temporal lobe cortex (MTLC) (Kordower et al., 2001).

In line with results on the contribution of myelin breakdown to AD pathology (Hyman et al., 1986; Wallin et al., 1989; Bartzokis, 2004), a further line of evidence suggests that alterations in white matter (WM) tracts which interconnect MTL structures occur before gray matter (GM) atrophy sets in and are also more severe in the preclinical phase of AD (De la Monte, 1989). Moreover, WM pathology was reported to be independent of regional cortical degeneration (Hyman et al., 1986; Delacourte et al., 1999; Kalus et al., 2006; Salat et al., 2010; Agosta et al., 2011).

Although significant neuropathological changes can be observed very early in the course of AD, it can be very difficult to diagnose aMCI since the associated cognitive deficits cannot easily be discriminated from the decline found in other cerebral disorders or in healthy aging (Petersen, 2004). However, while the memory deficits in AD are initially related to MTLC pathology, memory problems in healthy aging seem to be associated with the observed accelerated shrinkage of the hippocampus and prefrontal areas (Raz et al., 2005). In contrast, volume loss of the MTLC is minimal in healthy aging and only of a higher degree in very old age. Hence, neuropsychological tests that focus on cognitive functions relying on the integrity of the MTLC can provide an effective and sufficiently sensitive marker for an early diagnosis as those deficits should be different from deficits caused by healthy aging or other neurological or mental disorders. This may also promote early treatment allowing to slow down the progress of the disease by maintaining the patients' present cognitive level for a longer period of time.

In order to identify those neuropsychological tests which are most sensitive in diagnosing very early AD, Swainson et al. (2001) compared the performance of patients with mild AD, aMCI, major depression, and healthy controls on a range of tests including the CANTAB (Cambridge Neuropsychological Test Automated Battery). Scores on two CANTAB tests – paired associates learning (PAL) and delayed matching to sample (DMS) as well as performance on the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) logical memory recall task precisely classified participants to the AD or the control group. In addition, the CANTAB PAL and DMS test scores were correlated with the degree of global cognitive decline during an 8-month follow-up period. These same two tests together with logical memory recall, semantic naming, and a category fluency (CF) task were also sensitive to deficits in aMCI when compared to the control group. Also, Égerházi et al. (2007) used the CANTAB to examine the cognitive decline of patients with aMCI and AD and confirmed that especially performance on the PAL task is a very sensitive measure to detect early neuropathological symptoms that are related to AD. In another study, Fowler et al. (2002) showed that the decline in PAL and DMS performance within a 6-month interval predicts the progression from aMCI to AD within 2 years. The WMS-R subtest logical memory, which consists of two detailed stories that subjects have to freely recall and retell, was also shown to be very sensitive to early memory impairments. Rubin et al. (1998) reported that even at a time when clinical changes were not yet evident, older subjects who later converted to AD performed significantly poorer on this test than non-converters. However, the neural origin of the sensitivity of all these neuropsychological tests for aMCI and early AD remains to be specified. Moreover, the relationship between the extent of AD-related neuropathology in aMCI and the extent of mnemonic impairment is broadly unclear up to now.

A valuable source of information on the neural basis of this sensitivity can be provided by the investigation of the relationship between inter-individual differences in performance and differences in brain structure (Kanai and Rees, 2011). In order to relate the reported neuropsychological test impairments in aMCI and early AD to underlying morphological brain changes, we used VBM on structural neuroimaging data from subjects with single-domain aMCI. As neurofibrillary pathology in AD starts in the MTLC before reaching the hippocampus, we hypothesized that performance of those neuropsychological tests from the CANTAB and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus, Morris et al., 1989) batteries which are sensitive to aMCI and early AD [Boston naming test (BNT), CF, DMS, PAL, and WMS-R logical memory recall] is mainly related to the integrity of this brain region. Only patients with aMCI were investigated in order to counteract artificially modified correlations caused by group differences in regional brain volume and memory performance.

MATERIALS AND METHODS

SAMPLE

Twenty-five individuals (mean age 67.96 years, SD 4.36, range 61–75, five female) who met criteria for single-domain aMCI (Petersen et al., 1999; Winblad et al., 2004) took part in the study. Participants were recruited from the Memory Clinic of the Central Institute of Mental Health. The study was approved by the ethics committee of the Medical Faculty Mannheim, University of Heidelberg and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to study start.

CLINICAL ASSESSMENT

All patients were diagnosed after medical and neurological examination, clinical history, scoring on the Mini-Mental State Examination (MMSE), and after neuropsychological assessment with tests assessing psychomotor speed, attention, verbal fluency, executive functions, orientation, constructional praxis, and episodic memory taken from the CERAD, the CANTAB, and the WMS-R. In addition, all participants were screened for mental disorders by the German version of the Structured Clinical Interview for DSM-IV (SCID I, Wittchen et al., 1997). All participants were German native speakers. **Table 1** provides demographic characteristics and performance in neuropsychological tests. Additionally, the patient form of the Patient Competency Rating Scale (PCRS, Prigatano et al., 1986) and the PCRS relative's form (both forms were taken from the German PCRS analog Marburger Kompetenz-Skala, MKS, Gauggel, 1998) were used as measures for ratings of impairment of daily functioning. Participants also underwent a structural MRI examination. Images were screened for probable exclusion criteria by an experienced neuroradiologist.

Participants were diagnosed as having aMCI if they fulfilled the following criteria (Petersen et al., 1999; Winblad et al., 2004): (1) concerns about memory decline, corroborated by a patient's relative, (2) objective memory impairment defined by performance at

Table 1 | Demographics of the patient sample and mean scores for neuropsychological tests (standard deviation in parentheses, SD).

Number of subjects	25			
Mean age (years)	67.96	(4.36)		
Female/male	5/20			
Mean years of education (years)	11.28	(2.92)		
	Raw score	(SD)	Standard score*	(SD)
ASSESSMENT OF CLINICAL/GLOBAL FUNCTIONING				
Hamilton rating scale for depression (HAMD)	0.76	(1.27)	n/a	n/a
General depression scale (ADS-L)	7.92	(5.80)	−0.68	(0.82)
State – trait anxiety inventory – trait (STAI-T): total score	31.04	(8.25)	−0.36	(1.00)
Competence rating scale (patient form): functional abilities	102.72	(11.42)	n/a	n/a
Competence rating scale (patient form): cognitive abilities	46.56	(7.98)	n/a	n/a
Competence rating scale (relative's form): functional abilities	107.46	(8.07)	n/a	n/a
Competence rating scale (relative's form): cognitive abilities	50.00	(5.91)	n/a	n/a
Mehrfachwahl-Wortschatz-Intelligenztest-B (IQ-score)	101.84	(12.12)	0.16	(0.82)
CERAD: MMSE	28.16	(1.18)	−0.57	(0.99)
CANTAB simple reaction time: mean correct latency	250.36	(32.03)	n/a	n/a
ASSESSMENT OF MNEMONIC FUNCTIONING				
CANTAB delayed matching to sample test: percent correct (all delays)	78.93	(9.01)	0.15	(0.86)
CANTAB delayed matching to sample test: percent correct (12000 ms)	70.8	(17.30)	−0.03	(1.23)
CANTAB delayed matching to sample test: percent correct (4000 ms)	83.2	(11.44)	0.25	(0.78)
CANTAB paired associates learning test: total errors (6 shapes, adjusted)	9.12	(7.88)	0.06	(0.81)
CANTAB pattern recognition memory test: percent correct (immediate recall)	92.33	(9.89)	n/a	n/a
CANTAB pattern recognition memory test: percent correct (delayed recall)	74.00	(17.89)	n/a	n/a
CERAD: Boston naming test	14.28	(1.17)	0.35	(1.05)
CERAD: category fluency	20.44	(5.29)	0.29	(0.99)
Logical memory immediate (WMS-R)	31.52	(29.01)	31.52[a]	(29.01)
Logical memory delayed (WMS-R)	31.88	(29.58)	31.88[a]	(29.58)
ASSESSMENT OF EXECUTIVE FUNCTIONING				
CANTAB stockings of Cambridge: problems solved in minimum moves	7.6	(1.75)	−0.07	(0.90)

**Standard scores are z-values if not specified differently by a superscript letter.*

[a]The standardized mean is indicated by a percentile rank.

n/a Standardized scores are not available for these tests.

CANTAB, Cambridge Neuropsychological Test Automated Battery; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; WMS-R, Wechsler Memory Scale-Revised.

or lower than 1.3 SDs below the mean value (i.e., under the tenth percentile) of an age- and education-matched reference population on one or more memory tests, (3) preserved general cognitive functioning defined by performance at least above 1.3 SDs below the mean on all other measures not assessing memory, (4) independence of functioning in everyday life as assessed with the PCRS, (5) not demented or suffering from conditions that also may cause memory impairments as evaluated by MRI examination, medical history, and structured clinical interviews.

All participants were required to have a negative history for neurological disorders (e.g., stroke, cerebral neoplasm, hemorrhage, inflammation, Parkinson's disease, vascular encephalopathy with increased WM lesions), medical disorders (e.g., diabetes, untreated vitamin deficiencies, disorders of the thyroid, anemia, sleep apnea, other significant concurrent physical illnesses), and mental disorders (e.g., affective disorders). Current drug intake of dopaminergic or serotonergic agents, beta-adrenergic blockers, or benzodiazepines was ruled out. Additionally, all participants had to have normal or corrected to normal visual acuity and contrast sensitivity and had to be free of metallic biomedical implants (exclusion for MRI).

NEUROPSYCHOLOGICAL TESTS

Boston naming test

A short version of the BNT (Kaplan et al., 1983) is included in the CERAD testing battery. Participants are presented with 15 black-and-white line drawings for confrontation naming. If naming is not successful, a semantic, and if required, a phonetic cue is presented. We used the number of spontaneously correctly named items as the critical measure for the regression analyses.

Category fluency

In the CF task, participants have to name as many animals as possible in 1 min. The total number of items named in this interval was used in the analyses.

Wechsler memory scale – revised, logical memory

The WMS subtest logical memory consists of two detailed, thematically independent stories (25 items per story), that participants have to recall freely immediately after hearing and after a delay of 30 min. For analysis, we used the total number of recalled items in the immediate and in the delayed version.

Delayed matching to sample

The DMS assesses forced-choice recognition memory for novel visual patterns. Participants are confronted with a complex visual pattern. After a delay, this pattern is presented together with three similar patterns. The task is to identify which of these samples matches the target. The outcome measure used for regression analyses was the percentage of correct answers at the 4000 ms delay.

Paired associates learning

In this test, boxes are presented on the screen and opened in randomized order. A pattern is enclosed in one or more of them. Afterward, one pattern at a time is shown in the middle of the screen and the participant's task is to indicate the box where the pattern was initially placed. In case of an error, the patterns are presented again. Test difficulty increases in terms of the number of tested patterns. We used the adjusted score of total errors at the six-pattern stage in reversed polarity for analyses. In the Swainson et al. (2001) study, this outcome measure was shown to differentiate patients with mild AD from non-demented controls with 98% accuracy.

Pattern recognition memory

This is a two alternatives forced-choice recognition test with abstract visual patterns. During a study phase, the participant is presented with a series of 12 visual patterns. In the recognition phase, the participant is required to choose between a pattern already seen and a new one. The percentage of correct responses was used for regression analysis.

Stockings of Cambridge

The stockings of Cambridge (SOC) is a spatial planning test where participants are confronted with two displays containing three colored balls. The task is to copy the pattern shown in the upper display by moving the balls in the lower display. As an expression of overall executive planning accuracy, we used the outcome measure which contains the frequency of having successfully completed a test problem in the minimum possible number of moves (Robbins et al., 1998).

IMAGE ACQUISITION AND ANALYSIS

Structural MRI was acquired with a 3 Tesla magnetic resonance scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany). For each participant, a T1-weighted gradient echo MP-RAGE (Magnetization Prepared Rapid Gradient Echo) sequence (TR = 2300 ms, TE = 2.98 ms, flip angle 9°, FOV: 256 mm × 256 mm, voxel size: 1.0 mm × 1.0 mm × 1.1 mm, 160 sagittal slices) was acquired.

Voxel-based morphometry was applied to analyze correlations between neuropsychological test scores and GM and WM values. Contrary to manual tracing approaches, VBM permits to investigate the presence of structure-function relationships across the entire brain without *a priori* decisions about which structures to evaluate. This strategy allows to investigate if the critical tests were exclusively or especially sensitive to AD-related changes. Additionally, VBM is an automated, rater-independent method, and provides very reproducible results (Busatto et al., 2008). In contrast, the tracing procedure is dependent on unambiguous borders and anatomical landmarks and results are difficult to replicate between laboratories (Good et al., 2001). Data pre-processing and analysis were performed using SPM8[1] (Wellcome Department of Imaging Neuroscience, London, UK). Data pre-processing involved visual inspection of the T1-weighted images to control for imaging artifacts and the consecutive segmentation into GM, WM, and cerebrospinal fluid (CSF), building a customized template for GM and WM through an iteratively non-linear registration algorithm (DARTEL Toolbox for SPM8; Good et al., 2001; Ashburner, 2007) and a normalization of this template to the Montreal Neurological Institute template[2]. The Jacobian determinants resulting from the normalization procedure were used to obtain modulated VBM data preserving regional volumes. Individual GM and WM images were smoothed with an isotropic Gaussian kernel of 6 mm full-width at half-maximum before entering them into statistical analyses. Global volumes of GM, WM, and CSF were assessed from segmented images using the VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm8) and summed to generate an estimate for total intracranial volume (TIV). To correlate volumes and neuropsychological performance, separate test-wise regression analyses were calculated using raw scores of each test and GM and WM volumes, respectively. Age, gender, TIV as well as education were entered as covariates of no interest into all regression analyses. Results were considered significant if they consisted of at least 15 neighboring voxels that surpassed an uncorrected threshold of $p < 0.001$ (Forman et al., 1995). Given the poorer signal-to-noise ratio often observed in MTL regions due to susceptibility-related signal loss (e.g., Schacter and Wagner, 1999), a more liberal threshold of $p < 0.005$ was used for analyses within this region.

RESULTS

White matter regression analyses demonstrated various significant positive correlations with neuropsychological test scores from the CANTAB and CERAD batteries. Significant correlations with WM volume for tests from the visual memory domain [DMS, PAL, pattern recognition memory (PRM)] were widespread but accumulated in bilateral temporal lobes including parahippocampal WM. For WMS story recall, which reflects immediate and delayed verbal memory, significant correlations were found with WM volume in the bilateral parahippocampal gyri and the left precuneus. Semantic memory test scores (CF, BNT) and WM volume were significantly correlated in the left parahippocampal gyrus. Besides task and modality specific structure-function relationships along the entire parahippocampal gyrus, a high degree of overlap of the clusters from the independent VBM analyses was found in the vicinity of the left perirhinal cortex (see **Figure 1**; **Table 2**).

In contrast to the memory-dependent measures, performance scores of the SOC, reflecting executive functioning, revealed significant correlations with WM values localized in the left frontal lobe.

No coherent results were obtained in the regression analysis with regard to GM volumes.

[1] http://www.fil.ion.ucl.ac.uk/spm/software/spm8

[2] http://www.loni.ucla.edu/ICBM/ICBM_Databases.html

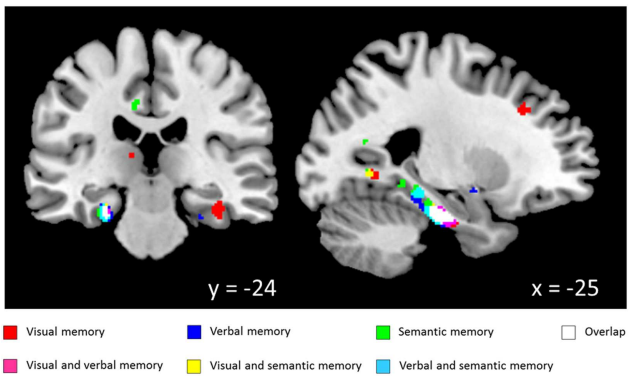


FIGURE 1 | Correlation between white matter volume and memory scores (coordinates in MNI space; thresholded at $p < 0.005$). *Visual memory*: paired associates learning, delayed matching to sample, pattern recognition memory; *Verbal memory*: Wechsler memory scale-revised, logical memory recall; *Semantic memory*: Boston naming test, category fluency.

DISCUSSION

The present study revealed the neural correlates of different cognitive sub-functions assessed by neuropsychological tests that are most commonly used for diagnosing aMCI and early AD. VBM analyses demonstrated that performance in a variety of mnemonic tests is directly related to the integrity of the MTLC in patients with single-domain aMCI. In more detail, performance in BNT, CF, PAL, DMS, PRM as well as WMS was mainly associated with reduced WM volume in the perirhinal and entorhinal region. Although no exact tract definition is possible using VBM-derived data, it is likely that the perforant path, which provides the major input route to the hippocampus as well as the cingulum bundle connecting the various components of the limbic system, are included in the reported MTLC WM clusters. In contrast, a significant association of measures of executive functioning and WM volume was found in the frontal lobe. Retrospectively, these tests were found to be sensitive to MCI and early AD in previous studies because they rely on the integrity of those brain structures which are specifically injured in these conditions. These findings are consistent with the specific pathology in the AD process (Hyman et al., 1986; Wallin et al., 1989; Bartzokis, 2004) and support the notion of a very early involvement of the MTLC during the disease process. Previous comparisons of MCI patients to healthy controls showed different forms of brain atrophy depending on the nature and state of the cognitive impairment (e.g., Whitwell et al., 2007). Interestingly, a cohort analysis revealed no decreases in GM and WM volumes in the MTL in our patients with aMCI. This might be due to the fact that they are at a very early stage of the disease process so that a subtle decline in regional GM and WM volume is not detectable yet, at least not when using VBM. Nevertheless, even in the absence of visible atrophy on MRI scans, the result of the regression analyses demonstrated a clear relationship between the mnemonic impairments and the integrity of the MTLC. This fits well to the results of a recent meta-analysis by Schmand et al. (2010) who concluded that memory impairment is a much more precise early predictor of AD than local brain atrophy. Recently, Leal and Yassa (2013) argued that the sensitivity of AD markers may vary as a function of how far patients are in the disease process with small changes in the perforant path being a much more salient feature than frank volume loss in the MTL in the early MCI phase. The authors concluded that in the absence of overt structural decline, functional markers are most important.

Contrary to our expectations, we could not observe a structure-function relationship with regard to GM. Similarly to the missing signs of clear MTLC atrophy in our patient sample, this might be caused by the very early state of the cognitive impairment. As mentioned above, alterations in WM tracts connecting MTL structures seem to occur before cortical degeneration starts and were also found to be partly independent of it (Delacourte et al., 1999; Kalus et al., 2006; Salat et al., 2010). In a postmortem investigation of very mild AD patients, Hyman et al. (1986) could demonstrate that cell loss in the MTLC causes a disconnection of the hippocampus from cortical inputs and that this disconnection was related to memory impairments. Recent diffusion tensor imaging and VBM studies confirmed that it is the MTLC WM that is affected most prominently in aMCI (Salat et al., 2010) and AD (Stoub et al., 2006) and that those alterations are related to later memory impairments (Salat et al., 2010). In addition, Zhuang et al. (2012) investigated retrospectively whether microstructural WM changes are already present in cognitively normal individuals without dementia who will later develop aMCI. At baseline, converters compared to non-converters showed substantial reductions in WM integrity in the MTLC whose degree was correlated with greater verbal episodic memory decline. In contrast, GM density was found not to be related to longitudinal episodic memory loss.

A considerable number of findings indicate that the involvement of the MTLC in binding seems both necessary and sufficient for the formation of semantic representations, i.e., semantic memories of events (e.g., Taylor et al., 2006). By binding associative or contextual information together with the semantic item representation, the hippocampus instead provides both necessary and sufficient conditions for the formation of episodic memories (e.g., Aggleton and Brown, 2006). However, due to this probable interruption of information flow between the different MTL structures, MTLC and hippocampus were not differently associated with semantic and episodic memory processes in our study. Although recall and cued recall tests normally rely more on the hippocampus (Golomb et al., 1994; Pohlack et al., 2013), performance in the WMS logical memory recall task or in the PAL were related to MTLC integrity in our sample. However, WM volume of different MTLC areas was differently associated with certain memory sub-functions with regard to laterality. Both PAL and DMS performance primarily correlated with WM volume in the area of the right parahippocampal gyrus while semantic memory as measured by CF and BNT was associated with left hemisphere WM volume.

Within this context, it is important to note that we did not identify the brain regions underlying the specific task-relevant cognitive processes *per se* as only participants in a pathological condition were investigated. Consequently, it is very likely that due to the probable disconnection of MTL structures, reorganization, or compensation processes are at work in aMCI patients.

Table 2 | Coordinates of peak value for clusters of white matter positively correlated with neuropsychological test performance.

Test score	Region	Hemisphere	Talairach coordinates			Cluster size	Peak *T*-value
			x	*y*	*z*	*k*	
DMS	Parahippocampal gyrus (uncus)	R	32	−4	−29	63	3.53*
	Temporal lobe (superior temporal gyrus)[a]	L	−45	−8	−7	78	4.47**
	Occipital lobe (Cuneus)[a]	L	−3	−83	25	60	4.39**
	Temporal lobe (middle temporal gyrus)	R	43	−45	6	45	3.93**
PAL	Parahippocampal gyrus	R	36	−26	−14	150	5.16**
	Frontal lobe (middle frontal gyrus)[a]	L	−38	17	25	39	4.46**
PRM	Parahippocampal gyrus	L	−23	−17	−17	87	5.11**
WMS_I	Parahippocampal gyrus	R	29	−23	−19	63	3.87*
	Parahippocampal gyrus	L	−26	−23	−21	177	5.71**
WMS_II	Temporal lobe (middle temporal gyrus)	L	−54	−7	−17	19	3.98*
	Parahippocampal gyrus	L	−23	−22	−19	119	4.56**
CF	Parahippocampal gyrus[a]	R	42	−21	−19	79	6.70**
BNT	Limbic lobe (uncus)	R	29	−4	−29	23	3.58*
	Parahippocampal gyrus	L	−24	−34	−5	45	3.46*
	Parahippocampal gyrus	L	−31	5	−30	51	6.19**
	Parahippocampal gyrus	L	−29	−18	−17	50	4.26**
	Temporal lobe (middle temporal gyrus)[a]	L	−27	−61	19	45	4.48**
	Temporal lobe (middle temporal gyrus)[a]	R	33	−55	22	24	4.26**
SOC	Frontal lobe (inferior frontal gyrus)[a]	L	−43	19	16	151	4.90**

$p < 0.005$ uncorrected for multiple comparisons.

**$p < 0.001$ uncorrected for multiple comparisons.*

[a]*For peak voxel coordinates that have been identified by the Talairach Daemon as sub-gyral, the nearest labeled gyrus/nucleus within a distance of 5 mm is given in parentheses.*

DMS, delayed matching to sample; PAL, paired associates learning; PRM, pattern recognition memory; WMS_I, Wechsler Memory Scale-Revised, logical memory immediate recall; WMS_II, Wechsler Memory Scale-Revised, logical memory delayed recall; CF, category fluency; BNT, Boston naming test; SOC, Stockings of Cambridge.

This precludes any clear inferences to intact cognitive processes in a normal healthy population. Here, we asked instead why specific neuropsychological tests have previously been found to be sensitive for aMCI and early AD.

Besides methodological differences, the position of our patients on a very early stage of the disease process may also account for different findings in the literature relating to the reported regression analyses (e.g., Schmidt-Wilcke et al., 2009). Chételat et al. (2003) found that deficits in both word list encoding and retrieval, were correlated with a decline in hippocampal GM in patients with single-domain aMCI. In contrast to our study, only GM density in patients diagnosed using a more conservative performance cut-off score (1.5 SDs instead of 1.3 SDs as in the present study) was used. This was also the case in a study by Barbeau et al. (2008) who reported that in aMCI patients with preserved recognition and impaired recall, GM density was reduced in frontal areas while aMCI patients with impaired recall and recognition memory showed reduced density in the right MTL and bilateral temporo-parietal regions. In addition, the diagnostic sensitivity of the tests applied in these investigations is so far unclear. A cohort analysis conducted by Schmidt-Wilcke et al. (2009) revealed bilateral decreases in GM density in the MTLs and the lateral temporal lobes when aMCI patients were compared to healthy controls. Additional regression analyses showed a significant positive association between immediate verbal recall and GM integrity in the left MTLC while delayed free recall correlated with GM density in the hippocampus proper. However, in this study also patients with multiple-domain aMCI were enrolled. This was also the case in a recent study by Barbeau et al. (2012) which demonstrated significant positive correlations between semantic memory scores and MTLC as well as anterior hippocampus GM density. However, as the kind of conversion of patients suffering from multiple-domain aMCI is less clear (Petersen, 2004; Fischer et al., 2007), these data are not directly comparable to the results of the present study that only incorporated patients with single-domain aMCI, who are probably located at a transitional stage toward the development of AD. Thus, the current results obtained in a more homogenous sample at a probable earlier time point in the disease process argue even more strongly in favor of the diagnostic value of the reported memory tests.

CONCLUSION

In a homogenous sample of patients with single-domain aMCI, we detected relationships between brain structure and mnemonic function in regions closely similar to previously established early morphological alterations in aMCI and AD even before those structural manifestations are detectable. By this, the present results suggest that performance in frequently used neuropsychological memory tests can predict the integrity of the cortical regions which are affected first by AD pathology such as the perirhinal cortex.

However, it should be kept in mind that this study also has some limitations. Due to the exploratory purpose of this study and the poorer signal-to-noise ratio often observed in MTL regions due to susceptibility-related signal loss, a more liberal threshold of $p < 0.005$ together with a cluster-threshold of at least 15 neighboring voxels was used for analyses within this region. When using FWE as correction, none of the results survived. Moreover, the present sample was diagnosed with the same tests that were used for regression analyses. In addition no control group was tested. Consequently, the observed correlations are not necessarily aMCI-specific. Nevertheless, they demonstrate why specific neuropsychological tests have previously been found to be sensitive for aMCI and early AD.

REFERENCES

Aggleton, J. P., and Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends Cogn. Sci. (Regul. Ed.)* 10, 455–463. doi:10.1016/j.tics.2006.08.003

Agosta, F., Pievani, M., Sala, S., Geroldi, C., Galluzzi, S., Frisoni, G. B., et al. (2011). White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* 258, 853–863. doi:10.1148/radiol.10101284

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113. doi:10.1016/j.neuroimage.2007.07.007

Barbeau, E., Didic, M., Joubert, S., Guedj, E., Koric, L., Felician, O. R., et al. (2012). Extent and neural basis of semantic memory impairment in mild cognitive impairment. *J. Alzheimers Dis.* 28, 823–837. doi:10.3233/JAD-2011-110989

Barbeau, E. J., Ranjeva, J. P., Didic, M., Confort-Gouny, S., Felician, O., Soulier, E., et al. (2008). Profile of memory impairment and gray matter loss in amnestic mild cognitive impairment. *Neuropsychologia* 46, 1009–1019. doi:10.1016/j.neuropsychologia.2007.11.019

Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol. Aging* 25, 5–18. doi:10.1016/j.neurobiolaging.2003.03.001

Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–259. doi:10.1007/BF00308809

Busatto, G. F., Diniz, B. S., and Zanetti, M. V. (2008). Voxel-based morphometry in Alzheimer's disease. *Expert Rev. Neurother.* 8, 1691–1702. doi:10.1586/14737175.8.11.1691

Busse, A., Hensel, A., Gühne, U., Angermeyer, M. C., and Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 67, 2176–2185. doi:10.1212/01.wnl.0000249117.23318.e1

Chételat, G., Desgranges, B., de la Sayette, V., Viader, F., Berkouk, K., Landeau, B., et al. (2003). Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 126, 1955–1967. doi:10.1093/brain/awg196

De la Monte, S. M. (1989). Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease. *Ann. Neurol.* 25, 450–459. doi:10.1002/ana.410250506

Delacourte, A., David, J. P., Sergeant, N., Buée, L., Wattez, A., Vermersch, P., et al. (1999). The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology* 52, 1158–1165. doi:10.1212/WNL.52.6.1158

Égerházi, A., Berecz, R., Bartók, E., and Degrell, I. (2007). Automated neuropsychological test battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 746–751. doi:10.1016/j.pnpbp.2007.01.011

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., et al. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* 68, 288–291. doi:10.1212/01.wnl.0000252358.03285.9d

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., and Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging fMRI: use of a cluster-size threshold. *Magn. Reson. Med. Sci.* 33, 636–647. doi:10.1002/mrm.1910330508

Fowler, K. S., Saling, M. M., Conway, E. L., Semple, J. M., and Louis, W. J. (2002). Paired associate performance in the early detection of DAT. *J. Int. Neuropsychol. Soc.* 8, 58–71. doi:10.1017/S1355617702811067

Gauggel, S. (ed.) (1998). *Marburger Kompetenz-Skala (MKS)*. Marburg: University of Marburg.

Golomb, J., Kluger, A., de Leon, M. J., Ferris, S. H., Convit, A., Mittelman, M. S., et al. (1994). Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. *Learn. Mem.* 1, 45–54.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K. J., and Frackowiak, R. S. J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14, 21–36. doi:10.1006/nimg.2001.0857

Hyman, B. T., Van Hoesen, G. W., Kromer, L. J., and Damasio, A. R. (1986). Perforant pathway changes and the memory impairment of Alzheimer's disease. *Ann. Neurol.* 20, 472–481. doi:10.1002/ana.410200406

Kalus, P., Slotboom, J., Gallinat, J., Mahlberg, R., Cattapan-Ludewig, K., Wiest, R., et al. (2006). Examining the gateway to the limbic system with diffusion tensor imaging: the perforant pathway in dementia. *Neuroimage* 30, 713–720. doi:10.1016/j.neuroimage.2005.10.035

Kanai, R., and Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nat. Rev. Neurosci.* 12, 231–242. doi:10.1038/nrn3000

Kaplan, E., Goodglass, H., Weintraub, S., and Segal, O. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

Karas, G. B., Scheltens, P., Rombouts, S. A., Visser, P. J., van Schijndel, R. A., Fox, N. C., et al. (2004). Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 23, 708–716. doi:10.1016/j.neuroimage.2004.07.006

Kordower, J. H., Chu, Y., Stebbins, G. T., DeKosky, S. T., Cochran, E. J., Bennett, D., et al. (2001). Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. *Ann. Neurol.* 49, 202–213. doi:10.1002/1531-8249(20010201)49:2<202::AID-ANA40>3.0.CO;2-3

Leal, S. L., and Yassa, M. A. (2013). Perturbations of neural circuitry in aging, mild cognitive impairment, and Alzheimer's disease. *Ageing Res. Rev.* doi:10.1016/j.arr.2013.01.006

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., et al. (1989). The Consortium to Establish a Registry for Alzheimer's Disease CERAD Part I clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 39, 1159–1165. doi:10.1212/WNL.39.9.1159

Pennanen, C., Kivipelto, M., Tuomainen, S., Hartikainen, P., Hänninen, T., Laakso, M. P., et al. (2004). Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol. Aging* 25, 303–310. doi:10.1016/S0197-4580(03)00084-8

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. doi:10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* 56, 303–308. doi:10.1001/archneur.56.3.303

Pihlajamäki, M., Jauhiainen, A. M., and Soininen, H. (2009). Structural and functional MRI in mild cognitive impairment. *Curr. Alzheimer Res.* 6, 179–185. doi:10.2174/156720509787602898

Pohlack, S. T., Meyer, P., Cacciaglia, R., Liebscher, C., Ridder, S., and Flor, H. (2013). Bigger is better! Hippocampal volume and declarative memory performance in healthy young men. *Brain Struct. Funct.* doi:10.1007/s00429-012-0497-z

Prigatano, G. P., Fordyce, D. J., Zeiner, H. K., Roueche, J. R., Pepping, M., and Wood, B. C. (1986). *Neuropsychological Rehabilitation after Brain Injury*. Baltimore: John Hopkins University Press.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb. Cortex* 15, 1676–1689. doi: 10.1093/cercor/bhi044

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., Lawrence, A. D., McInnes, L., et al. (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J. Int. Neuropsychol. Soc.* 4, 474–490.

Rubin, E. H., Storandt, M., Miller, J. P., Kinscherf, D. A., Grant, E. A., Morris, J. C., et al. (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Arch. Neurol.* 55, 395–401. doi:10.1001/archneur.55.3.395

Salat, D. H., Tuch, D. S., van der Kouwe, A. J., Greve, D. N., Pappu, V., Lee, S. Y., et al. (2010). White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiol. Aging* 31, 244–256. doi: 10.1016/j.neurobiolaging.2008.03.013

Schacter, D. L., and Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9, 7–24. doi: 10.1002/(SICI)1098-1063(1999)9:1<7::AID-HIPO2>3.0.CO;2-K

Schmand, B., Huizenga, H. M., and van Gool, W. A. (2010). Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer's disease. *Psychol. Med.* 40, 135–145. doi:10.1017/S0033291709991516

Schmidt-Wilcke, T., Poljansky, S., Hierlmeier, S., Hausner, J., and Ibach, B. (2009). Memory perdormance correlates with gray matter density in the ento-/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls – a voxel based morphometry study. *Neuroimage* 47, 1914–1920. doi: 10.1016/j.neuroimage.2009.04.092

Stoub, T. R., deToledo-Morrell, L., Stebbins, G. T., Leurgans, S., Bennett, D. A., and Shah, R. C. (2006). Hippocampal disconnection contributes to memory dysfunction in individuals at risk for Alzheimer's disease. *Proc. Natl. Acad. Sci. U.S.A.* 103, 10041–10045. doi: 10.1073/pnas.0603414103

Swainson, R., Hodges, J. R., Galton, C. J., Semple, J., Michael, A., Dunn, B. D., et al. (2001). Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dement. Geriatr. Cogn. Disord.* 12, 265–280. doi: 10.1159/000051269

Taylor, K. I., Moss, H. E., Stamatakis, E. A., and Tyler, L. K. (2006). Binding crossmodal object features in perirhinal cortex. *Proc. Natl. Acad. Sci. U.S.A.* 103, 8239–8244. doi:10.1073/pnas.0509704103

Wallin, A., Gottfries, C. G., Karlsson, I., and Svennerholm, L. (1989). Decreased myelin lipids in Alzheimer's disease and vascular dementia. *Acta Neurol. Scand.* 80, 319–323. doi:10.1111/j.1600-0404.1989.tb03886.x

Wechsler, D. (1987). *Wechsler Memory Scale-Revised*. New York: Harcourt Brace Jovanovich.

Whitwell, J. L., Petersen, R. C., Negash, S., Weigand, S. D., Kantarci, K., Ivnik, R. J., et al. (2007). Patterns of atrophy differ among specific subtypes of mild cognitive impairment. *Arch. Neurol.* 64, 1130–1138. doi:10.1001/archneur.64.8.1130

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J. Intern. Med.* 256, 240–246. doi:10.1111/j.1365-2796.2004.01380.x

Wittchen, H. U., Wunderlich, U., Gruschwitz, S., and Zaudig, M. (1997). *SKID-I. Strukturiertes Klinisches Interview für DSM-IV*. Göttingen: Hogrefe.

Yaffe, K., Petersen, R. C., Lindquist, K., Kramer, J., and Miller, B. (2006). Subtype of mild cognitive impairment and progression to dementia and death. *Dement. Geriatr. Cogn. Disord.* 22, 312–319. doi: 10.1159/000095427

Zhuang, L., Sachdev, P. S., Trollor, J. N., Kochan, N. A., Reppermund, S., Brodaty, H., et al. (2012). Microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI. *Neurology* 79, 748–754. doi: 10.1212/WNL.0b013e3182661f4d

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Retrieval of recent autobiographical memories is associated with slow-wave sleep in early AD

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Autobiographical memory is commonly impaired in Alzheimer's disease (AD). However, little is known about the very recent past which is though highly important in daily life adaptation. In addition, the impact of sleep disturbances, also frequently reported in AD, on the consolidation, and retrieval of autobiographical memories remains to be assessed. Using an adaptation of the TEMPau task, we investigated the neural substrates of autobiographical memory for recent events and the potential relationship with sleep in 14 patients with mild AD. On day 1, autobiographical memory was explored across three periods: remote (18–30 years), the last 2 years and the last month. After testing, sleep was recorded using polysomnography. The next day, AD patients benefited a resting-state ^{18}FDG-PET scan and a second exploration of autobiographical memory, focusing on the very recent past (today and yesterday). Total recall and episodic recall scores were obtained. In addition, for all events recalled, Remember responses justified by specific factual, spatial, and temporal details were measured using the Remember/Know paradigm. Retrieval of autobiographical memories was impaired in AD, but recall of young adulthood and very recent events was relatively better compared to the two intermediate periods. Recall of recent events (experienced the day and the day preceding the assessment) was correlated with brain glucose consumption in the precuneus and retrosplenial cortex, the calcarine region, the angular gyrus, and lateral temporal areas. AD patients also provided more Justified Remember responses for events experienced the previous-day than for those experienced the day of the assessment. Moreover, Justified Remember responses obtained for events experienced before sleep were positively correlated with the amount of slow-wave sleep. These data provide the first evidence of an association between the ability to retrieve recent autobiographical memories and sleep in mild AD patients.

Keywords: Alzheimer's disease, sleep, autobiographical memory, memory consolidation, PET

INTRODUCTION

Autobiographical memory is a multifaceted concept which concerns information and experiences of one's personal life and gives a sense of self-continuity (Piolino et al., 2009). Based on the observation of the amnesic patient KC, Tulving et al. (1988) proposed to distinguish within autobiographical memory an episodic component (altered in KC), containing personal specific events, situated in time and space ('*the day I had this car accident*'), and a semantic component, termed personal semantic memory (preserved in KC), storing general knowledge about our past such as the names of colleagues, generic events ('*summer holidays at Sainte Marine*'), and self-concepts. Autobiographical memory is subserved by a core neural network, mainly left-sided, including the medial and ventrolateral prefrontal cortex, medial, and lateral temporal areas, the retrosplenial/posterior cingulate cortex, the temporoparietal junction, and the cerebellum (Maguire, 2001; Conway et al., 2002; Svoboda et al., 2006; Cabeza and St Jacques, 2007; Martinelli et al., 2013a).

In the present study, we were interested in the assessment of recent episodic autobiographical memories and in the brain areas supporting their retrieval. We also investigated the impact of sleep on memory recall.

Numerous studies documented a general impairment of autobiographical memory in Alzheimer's disease (AD) (Kopelman et al., 1989; Greene and Hodges, 1996; Addis and Tippett, 2004; Ivanoiu et al., 2004; Irish et al., 2011). Most of them showed a temporally graded retrograde amnesia, with memories from the young adulthood period being better preserved than recent

ones (a phenomenon well-known as the "reminiscence bump," Rubin et al., 1986). By distinguishing both components of autobiographical memory, a dissociation emerged in AD. Thus, Piolino et al. (2003), using a semi-structured questionnaire (TEMPau) assessing the ability to recollect detailed specific events situated in time and space from different periods covering the entire lifespan (from childhood/teenage to the last 12 months), they showed that retrieval of strictly episodic autobiographical memories (i.e., unique, specific in time and space, and detailed) is impaired in AD patients whatever the time period. Patients also exhibited a deficit of autonoetic consciousness, defined as the feeling of re-experiencing or reliving the past and mentally traveling back in subjective time. Contrasting with this impairment of episodic autobiographical memories, Martinelli et al. (2013b) documented a preservation of personal semantic memory assessed by asking AD patients to recall generic events memory. However, other studies reported a temporally graded deficit of personal semantic memory, with a relative preservation of the most recent information (Kopelman et al., 1989; Addis and Tippett, 2004). Greene et al. (1995) reported a similar deficit whatever the time period explored while Ivanoiu et al. (2004) observed a deficit with only a modest temporal gradient.

Several authors tried to disclose the brain areas whose atrophy or dysfunction may explain the impairment of autobiographical memory in AD. Thus, Gilboa et al. (2005) reported that episodic autobiographical memory was associated with the volume of the medial temporal lobes and the anterior lateral temporal neocortex. Interestingly, this pattern of correlation was invariant whatever the remoteness of memories suggesting that the integrity of medial temporal lobes is crucial for the retrieval of episodic autobiographical memories regardless of their age. In contrast, deficits of personal semantics were related to the atrophy of anterior and posterior lateral temporal areas bilaterally, more pronounced on the left, as well as right frontal degeneration. More recently, Philippi et al. (2012) reported positive correlations between hippocampal volume and episodic autobiographical memory for both recent and remote periods of life. Using the TEMPau task exploring autobiographical memory from three time periods (the last 5 years, middle age, teenage/childhood) and resting-state FDG-PET imaging, Eustache et al. (2004) reported a temporal gradient of recalls in favor of remote past and that right hippocampal metabolism correlated uniquely with recent memories. In addition, retrieval of recent memories was preferentially associated with right prefrontal cortex metabolism whereas remote memories relied more upon left prefrontal areas. According to the HERA model (Tulving et al., 1994), the right prefrontal cortex is more involved in episodic memory retrieval and the left in semantic memory retrieval. In this respect, the results reported by Eustache et al. (2004) support the idea that many autobiographical memories become "semanticized" over time and that preserved remote memories in AD patients are predominantly semantic by nature, even if some remote episodic memories can persist in these patients. In an fMRI study, Meulenbroek et al. (2010) contrasted the patterns of brain activity during retrieval of episodic autobiographical memories and during the processing of semantic information. They reported evidence of compensatory activations, notably within frontal areas, when AD patients retrieved episodic autobiographical memories. These compensatory activations in areas known to be involved in semantic processing, suggest that autobiographical memory would undergo an exaggerated shift from an episodic to a semantic content in AD.

Another aim of our study was to investigate the impact of sleep on the recall of autobiographical memories. Even if consolidation of freshly acquired memory traces can last months or years, it is well established that this process preferentially occurs during sleep and that the first post-learning night is crucial (Born et al., 2006). This has been demonstrated across a wide range of tasks for both procedural and episodic memories (Rauchs et al., 2005; Diekelmann and Born, 2010). In our laboratory, we have shown that both slow-wave sleep and Rapid-Eye Movement (REM) sleep are necessary for the consolidation of rich, vivid episodic memories. In particular, REM sleep favors the consolidation of the encoding context associated to the items (Rauchs et al., 2004). In addition, several studies indicate that sleep-dependent consolidation of episodic memories may be altered in older adults (Harand et al., 2012 for review) and we also reported correlations between sleep parameters and episodic memory performance in mild AD patients (Rauchs et al., 2008; Hot et al., 2011). Retention of recent personal episodic memories (e.g., memories of a recent conversation with a relative) was probed after sleep or an equivalent period of wakefulness in older adults (Aly and Moscovitch, 2010), but this issue has never been addressed in AD patients.

To sum up, episodic autobiographical memory is impaired in AD, even in the early stages of the disease (Murphy et al., 2008; Leyhe et al., 2009; Irish et al., 2010, 2011; Bastin et al., 2012). This deficit is mainly subserved by the dysfunction or degeneration of medial temporal areas. In most of the studies aforementioned, the exploration of the recent past was conducted on a period generally lasting about 1–5 years, completely neglecting the very recent past. In the present study, we explored episodic autobiographical memories experienced the day and the day preceding the assessment as well as memories dating back 2 years ago and the young adulthood period. The originality of this study also relies on the fact that our experimental design allowed us to control the events participants experienced and recalled, as they were present, most of the time, in the laboratory. A first aim of this study was therefore to precise, using resting-state ^{18}FDG-PET, the neural substrates of retrieval of recent autobiographical memories. We also aimed at investigating the impact of sleep on the recall of autobiographical memories, and expected to find significant correlations between indices of sleep quality and/or quantity (such as time spent in slow-wave sleep or REM sleep) and episodic autobiographical memories.

MATERIALS AND METHODS

PARTICIPANTS

Fourteen unmedicated, newly diagnosed AD patients (eight women, six men; mean age ± SD: 77.1 ± 4.1 years) with a MMSE score (Folstein et al., 1975) of 21 or higher (mean ± SD: 24.9 ± 2) participated in this study. Some data of most of these patients were previously published in two other studies (Rauchs et al., 2008; Hot et al., 2011). They were all recruited through a memory clinic, and all complained of memory impairment. They were selected on the basis of a neurological examination and a neuropsychological assessment, using the National Institute of Neurological and

Communicative Disorders and Stroke and the AD and Related Disorders Association criteria for probable AD (McKhann et al., 1984). At the time of the study, none of the patients was being or had been treated with specific medication, such as antiacetylcholinesterase agents. None of them suffered from sleep disorders such as periodic limb movement disorder or sleep apnea, confirmed by polysomnography.

Autobiographical memory scores of AD patients were compared to those obtained in a group of 14 age-matched healthy controls (9 women, 5 men; mean age ± SD: 75.1 ± 4.6 years) recruited in clubs for retired people. They had no neurological or psychiatric disorders. The mean score (±SD) for the MMSE was 29.4 (±0.9). These subjects were also paired according to their level of education with AD patients.

All subjects were right-handed, native French speakers and gave their written consent to the study after detailed information was provided to them and to a member of their family. The study was done in-line with the Declaration of Helsinki following approval by the Regional Ethics Committee.

GENERAL PROCEDURE

The general procedure is illustrated in **Figure 1**. Autobiographical memory for the very recent past (events experienced the day and the day preceding the assessment) was explored and compared to three other periods covering the young adulthood to the last month. On the first day, participants came to the hospital for a sleep recording. Before placement of electrodes, they performed the first part of the autobiographical memory (TEMPau) task assessing the three remote periods. Sleep was then recorded using standard polysomnography. The next morning, AD patients benefited an ^{18}FDG-PET scan to measure brain glucose consumption at the resting-state. In the evening, the second part of the TEMPau task, assessing the very recent past, was proposed to patients and controls together with other episodic memory tasks not described here but whose results have been published elsewhere (Rauchs et al., 2007, 2008; Hot et al., 2011).

MEMORY TESTING

We used an adaptation of the autobiographical memory task "TEMPau" developed by Piolino et al. (2003, 2009). This task, consisting of a semi-structured questionnaire, assesses the ability to recall detailed specific events situated in time and space from four time periods [P1: young adulthood (18–30 years), P2: the last 2 years (except the last month), P3: the last month, and P4: today and yesterday] as well as the subjective states of consciousness associated with those memories (Tulving, 1985, 2002).

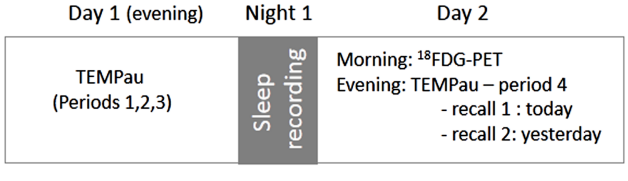


FIGURE 1 | Experimental design. Period 1: young adulthood (18–30 years), period 2: last 2 years (except the last month), period 3: last month, period 4: today and yesterday. Note that only AD patients benefited the PET examination.

For the most recent period (P4), participants had to recall what they did yesterday and today. More precisely, they were invited to relate a particular moment in the day, giving details about the chronology of the event, the place where it occurred and the people that were present.

For the three other periods, participants were invited to recall two personal events corresponding to two topics: (i) a meeting or an event associated to a person and (ii) a trip or journey. For each period, participants were invited to give details of a particular event. If a participant could not spontaneously recollect a specific event, cues were provided (for example, "on a day with a teacher or friend"), while he or she was encouraged to be specific if the memory was generic (e.g., "do you remember a particular day during this summer?"). After three cueing and/or encouragement attempts, the experimenter switched to the following topic or period.

Immediately after each recall, the participants were asked to indicate the subjective state of consciousness associated with the recall of *what* happened (i.e., the factual content), *where* (the place), and *when* (the moment). They were instructed to give a Remember, Know, or Guess response (Mäntylä, 1993) according to whether each of these three aspects of the recalled event was associated with conscious recollection, simply knowing, or guessing, respectively. A Remember response is defined as the ability to mentally relive specific aspects such as perceptions, thoughts, or feelings that occurred or were experienced at the time of the event. The participants were asked to give details aloud to ensure that they were using Remember responses properly. A Know response reflects simply knowing what happened, where and when, but this knowledge is not accompanied by any conscious recollection. A Guess response corresponds to aspects of the event that were neither consciously recollected nor simply known.

For the first three periods (P1, P2, and P3), the control of the veracity of the events recalled was made with the spouse/husband or a relative. For P4, we could perform a more stringent control of the events recalled by participants as they were present, most of the time, in the laboratory.

Each recalled event was scored on a four-point episodic scale based on that used by Baddeley and Wilson (1986). This scale takes into account the specificity of the memory (single or repeated event), the time, and spatial location, and the presence of details (perceptions, thoughts, or feelings). A specific event detailed and situated in time and space was given a score of 4 points. A specific event without any detail but located in time and space scored 3 points. A repeated or extended event scored 2 points or 1, depending on whether or not it was situated in time and space. Absence of memory or general information about the topic scored 0. The critical factor that allowed us differentiating specific events (scores 3 points) from a specific, detailed event (scored 4) was the failure, despite much encouragement, to add details concerning the source of acquisition. Recalled events scored 2 or 1 referred rather to personal semantic memory.

Two independent experts (GR and PP) rated each memory recalled and any difference of opinion between them was discussed until a consensus was reached. Two main scores were calculated

for each period: (i) an overall autobiographical memory score, named hereafter "total recall score," taking into account all types of recall, both specific and generic (maximum = 8 points for each period) and (ii) a strictly episodic recall referring to the recall of a specific memory, situated in time and space and with phenomenological details (perceptions, emotions, thoughts, mental images, . . .; maximum = 8 points for each period).

In addition, we also calculated a Remember score (*R*, maximum = 6 for each period) for the total number of *R* responses provided, irrespective of the kind of information (what, where, when) of each period and (iii) a justified Remember score (justified *R*, maximum = 6 for each period) for the number of *R* responses effectively associated with the recollection of a single event, with contextual details (thoughts, feelings, or perceptions for content, location for place, and time of day or temporal sequence for date).

SLEEP RECORDING

For all subjects, sleep was recorded in the sleep laboratory using a Nicolet Acquisition System, including continuous recordings of EEG, electro-oculogram, electro-myogram recorded at the chin, and electrocardiogram. EEG activity was recorded from right and left central (C3/C4), temporal (T3/T4), and occipital (O1/O2) derivations of the extended 10–20 international system (Nuwer et al., 1999), using Ag/AgCl electrodes with a vertex ground and a right ear reference. The impedance for all electrode sites was kept below 10 kΩ. The EEG filter band pass was 0.03–35 Hz and was digitized at 125 Hz.

Three additional electrodes were placed at the outer canthus and supraorbitally to the right eye with a bipolar recording for electro-oculogram activity. Sleep recordings were scored by an experienced physician (FB) according to standard criteria (Iber et al., 2007). Total sleep time, sleep onset latency, sleep efficiency, and the time and percentage of time spent in each sleep stage were determined.

PET METHODOLOGY

In the morning of day 2, all the patients underwent a resting PET examination using [^{18}F] Fluoro-2-deoxy-D-glucose (^{18}F-FDG). Data were collected using the high-resolution PET device ECAT Exact HR+ with isotropic resolution of 4.6 mm × 4.2 mm × 4.2 mm (field of view = 158 mm). The patients were fasted for at least 4 h before scanning. The head was positioned on a headrest according to the cantho-meatal line and gently restrained with straps. ^{18}F-FDG uptake was measured in the resting condition, with eyes closed, in a quiet and dark environment. A catheter was introduced in a vein of the arm for radiotracer administration. Following ^{68}Ga transmission scans, 3–5 mCi of ^{18}F-FDG were injected as a bolus at time 0, and a 10-min PET data acquisition period was begun at 50 min post-injection. Sixty-three planes were acquired with septa out (volume acquisition), using a voxel size of 2.2 mm × 2.2 mm × 2.43 mm (*x*, *y*, *z*). During PET data acquisition, head motion was monitored continuously with laser beams.

Preprocessing of FDG-PET data included (1) voxel-wise correction for partial volume effects (PVE) using the corresponding structural T1 MRI with the PMOD software (PMOD Technologies Ltd., Adliswil, Switzerland), (2) coregistration onto corresponding T1 MRI and spatial normalization to the MNI space using the parameters estimated from the corresponding T1-weighted MRI using the voxel-based morphometry 5.1 (VBM) toolbox (http://dbm.neuro.uni-jena.de) implemented in statistical parametric mapping 5 (SPM 5) software (Wellcome Trust Centre for Neuroimaging, London, UK), (3) quantitative scaling using the cerebellum gray matter as a reference to obtain standardized uptake value ratio (SUVr) images (cerebellum gray matter values were obtained for each participant using the cerebellum defined in the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), (4) smoothing with a 12-mm FWHM Gaussian kernel to blur individual variations in gyral anatomy and to increase signal-to-noise ratio, and (5) masking to exclude non-gray matter voxels. The resulting images were then used in the correlation analyses described below.

DATA ANALYSES

Analyses focused on the recent past (P4), the three other periods being used as control data for behavioral analyses. Memory scores obtained with the TEMPau task were analyzed using analyses of variance (ANOVA) with group (AD vs. controls) as between-subject factor and periods (P1, P2, P3, and P4) as within-subject factor. These analyses were followed by *post hoc* tests (HSD Tukey) when applicable. As the two memories of the most recent period (P4) were experienced on two different days, separated by a night during which sleep was recorded, we conducted similar analyses dividing the period P4 in two subperiods: yesterday and today. These analyses will allow to determine whether sleep has a beneficial effect on consolidation of autobiographical in AD patients and older adults. In addition, we also looked for correlations between sleep parameters (such as the percentage of time spent in each sleep stage) measured during the night and the memory score for the event experienced the previous-day.

Then, we investigated the neural substrates of recent memories in AD patients. To do so, correlations between the total recall score obtained for period P4 and brain metabolism were searched using SPM and Pearson's correlation test. Only the positive correlations (i.e., in the neurobiologically expected direction) were assessed, using a statistical threshold (uncorrected for multiple tests) of $p < 0.001$ for the voxels, to limit the number of statistical tests and the attending risk of false positives.

RESULTS

AUTOBIOGRAPHICAL MEMORY SCORES

Here is an example of what an AD patient related for the "yesterday" sub-period, describing his arrival at the hospital, the exploration of the remote period during the TEMPau task and the preparation for the sleep recording: "*Monday, in the afternoon, I prepared my belongings and the papers you need. I ate alone. I came to this hospital in the evening with my daughter. We came by car and left the house at about 7:45 pm. I performed some tests with you and we discussed about my life when I was a young man. It lasted more than 30 minutes. Then, two nurses (a man and a woman) put electrodes on my head. During the night, I found that the bed was too high and I felt cold.*"

The total recall score for this event was 3 (as it was a specific event, located in time and space, but without sufficient details). Indeed, he could not recall any details about the specific spatial context (the places where the different examinations occurred, his position in the room . . .), giving only general information (name of the city and the hospital). Thus, while the patient provided three Remember responses, only *R* responses associated with factual and temporal were justified.

Figure 2 illustrates the results for the total recall score, the strictly episodic recall score, as well as for the number of *R* and justified *R* responses in AD patients and controls across the four time periods. An ANOVA with period (P1, P2, P3, and P4) as within-subject factor and group as between-subject factor, performed on the total recall score revealed a significant main effect of group [$F(1,25) = 31.5$, $p < 0.0001$] and time period [$F(3,75) = 10.8$, $p < 0.0001$]. The group by period interaction was not significant [$F(3,75) = 1.72$, $p > 0.17$]. To further investigate the effect of time period, *post hoc* comparisons (HSD Tukey) were conducted and revealed that memory scores in both groups were not different for P1 and P4 ($p > 0.97$) and higher to those obtained for P2 and P3 (all p values < 0.002), indicating the existence of a reminiscence bump (P1) and a recency effect (P4). Performance on P2 and P3 did not differ significantly ($p > 0.99$). As we hypothesized a relative preservation of the very recent past in AD, we further investigated the effect of group according to the period. Group differences were observed for P2, P3, P4 (all p values < 0.05), patients scoring lower than controls, but not for P1 ($p > 0.39$).

A similar analysis conducted on the strictly episodic recall score revealed similar main effects [group: $F(1,25) = 12.9$, $p < 0.001$; period: $F(3,75) = 4.99$, $p < 0.003$] but no group by period interaction [$F(3,75) = 1.7$, $p > 0.17$]. *Post hoc* comparisons revealed that, in the whole group of participants, scores for P1, P2, and P4 were not significantly different (all p values > 0.26) while scores for P3, corresponding to the last month, were significantly lower than those for P4 ($p < 0.006$) and P1 ($p < 0.02$). A group difference was only observed for P4 ($p < 0.05$).

An ANOVA conducted on the number of Remember responses provided during memory recall revealed significant main effects of group [$F(1,25) = 17.45$, $p < 0.001$] and time period [$F(3,75) = 5.75$, $p < 0.001$] as well as a significant interaction between both factors [$F(3,75) = 3.27$, $p = 0.026$]. The number of Remember responses was stable across periods (all p values > 0.94) in controls, while AD patients provided more Remember responses for P1 and P4 (without any difference between them) than for P2 and P3 (all p values < 0.006, no difference between P2 and P3). Only scores for the two intermediate periods (P2, P3) significantly differed between groups (all p values < 0.01).

Finally, concerning the number of Remember responses justified by phenomenological details, the ANOVA revealed significant main effects of group [$F(1,25) = 23.49$, $p < 0.001$] and period [$F(1,25) = 14.3$, $p = 0.005$], but no interaction between these factors [$F(3,75) = 0.83$, $p > 0.48$]. A *post hoc* analysis conducted to further examine the effect of period revealed exactly the same pattern of results than for Remember responses (P1 = P4 > P2 = P3). Here again, only scores for the two intermediate periods (P2, P3) differed between AD patients and controls (all p values < 0.05).

Then, we conducted similar analyses dividing P4 into two sub-periods corresponding to yesterday and today events (**Figure 3**). These analyses revealed for the total recall score, the strictly episodic score and the number of Remember responses a main effect of group (all p values < 0.03), but no effect of sub-period or interaction between both factors. In contrast, for the number of justified Remember responses, we reported a main effect of group [$F(1,25) = 9.3$, $p = 0.005$] and a main effect of sub-period [$F(1,25) = 8.7$, $p = 0.007$]. The group by sub-period interaction was not significant [$F(1,25) = 0.95$, $p > 0.33$]. These results

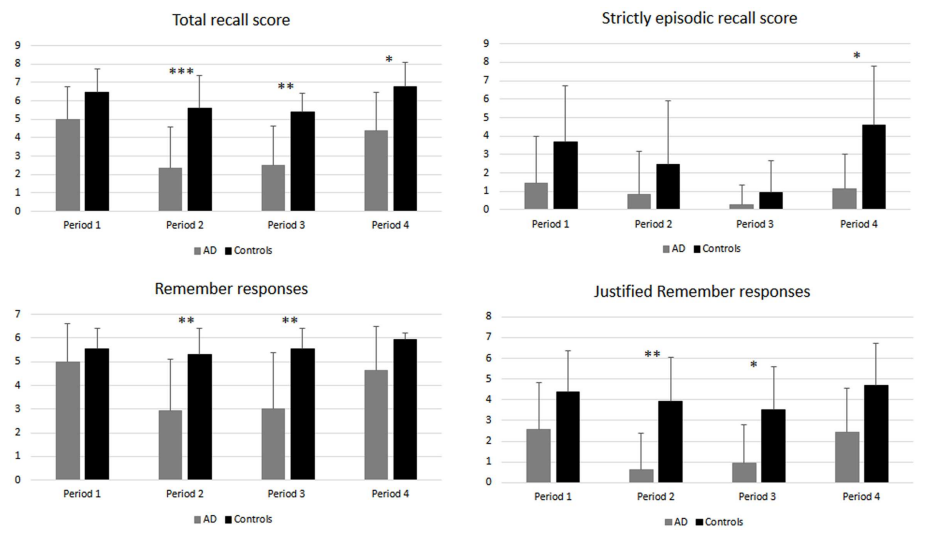


FIGURE 2 | Autobiographical memory scores in AD patients and healthy controls for the four time periods. Stars indicate between group differences. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

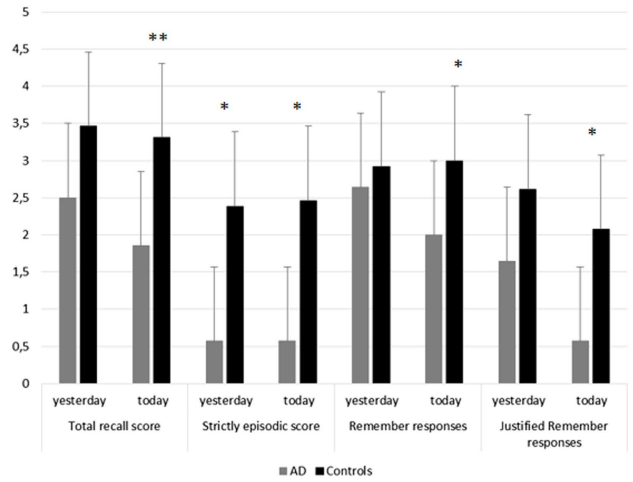


FIGURE 3 | Memory performance for yesterday and today events in AD patients and controls. This figure illustrates performance in AD patients and controls for each memory score (total recall score, strictly episodic recall score, number of Remember responses, number of justified Remember responses) for the recent period (P4), distinguishing yesterday, and today sub-periods. Stars indicate between group differences. $*p < 0.05$; $**p < 0.01$.

indicate that AD patients have lower scores than controls, and that in both groups, the number of justified Remember responses was higher for the events experienced the previous-day compared to today. These data suggest a beneficial effect of sleep on subsequent retrieval of recent autobiographical memories in mild AD patients.

SLEEP PARAMETERS

Sleep parameters in both groups are reported in **Table 1**. Group comparisons revealed that AD patients made significantly more sleep stage 1 than controls ($p < 0.01$) and tended to spent less time in slow-wave sleep ($p = 0.072$).

CORRELATIONS BETWEEN AUTOBIOGRAPHICAL MEMORY SCORES AND SLEEP PARAMETERS

Finally, we searched for correlations, in AD patients, between sleep parameters and memory scores corresponding to events that occurred on day 1 ("yesterday" sub-period). Due to a technical recording problem, sleep scoring was not possible in one patient, which was removed from this correlation analysis.

We observed significant positive correlations between the number of justified Remember responses and the percentage of time spent in slow-wave sleep ($r = 0.55$, $p < 0.05$), especially sleep stage 4 ($r = 0.60$; $p < 0.05$; **Figure 4**).

CORRELATIONS BETWEEN AUTOBIOGRAPHICAL MEMORY AND RESTING-STATE BRAIN GLUCOSE CONSUMPTION

Correlations analyses between autobiographical memory scores and resting-state brain glucose consumption were conducted in the group of AD patients and only for the most recent period (P4). One patient did not benefit the PET examination and was excluded from these analyses. In addition, correlations were only searched for the total recall score due to a very limited inter-subject variability for the other measures. Thus, the total recall score positively correlated with brain glucose consumption in the precuneus bilaterally extending to the retrosplenial cortex, the calcarine region, the angular gyrus as well as middle temporal gyri (**Table 2** and **Figure 5**). Then, we conducted similar analyses dividing P4 in two sub-periods corresponding to "yesterday" and "today." The pattern of correlations between brain glucose consumption and memory scores for the "yesterday" period was very similar to that reported above. In contrast, for "today" events, correlations were only found in the precuneus but at a more permissive statistical threshold ($p < 0.005$).

Table 1 | Sleep parameters in AD patients and controls.

	AD patients ($n = 13$)	Controls ($n = 14$)
GLOBAL PARAMETERS		
Time in bed (min)	531.2 ± 77.1	495.3 ± 48.7
Sleep period time (SPT, min)	504 ± 79.1	477.9 ± 46.9
Total sleep time (TST, min)	387.3 ± 91.2	385.2 ± 68.5
Sleep latency (min)	27.3 ± 33.9	17.5 ± 19.8
Sleep efficiency (%)	72.3 ± 10.9	77.7 ± 10.5
WASO (min)	23.7 ± 10.1	19.6 ± 9.3
SLEEP ARCHITECTURE (% SPT)		
Stage 1	18.2 ± 5.4[a]	13.1 ± 4.4
Stage 2	26.7 ± 7.7	31.2 ± 7.5
SWS	18.7 ± 7.7[b]	23.5 ± 5.5
REM sleep	12.6 ± 6.5	12.6 ± 6

Sleep period time corresponds to time in bed – sleep latency.
SWS, slow-wave sleep.
[a] $p < 0.01$;
[b] $p = 0.072$.

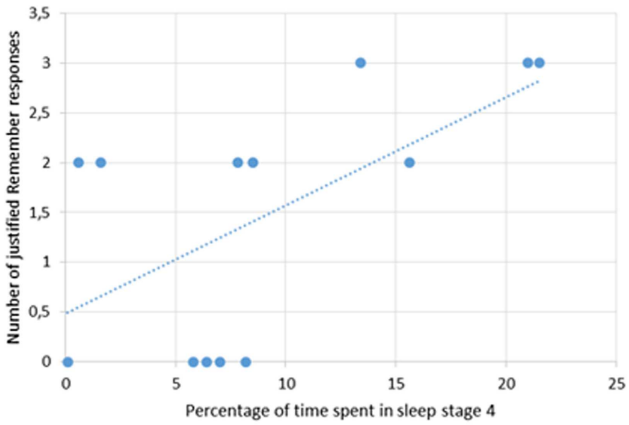


FIGURE 4 | Correlation between the number of justified Remember responses for the yesterday sub-period and the percentage of time spent in sleep stage 4 in AD patients.

DISCUSSION

The present study was designed to investigate autobiographical memory in patients with mild AD, focusing on the very recent past.

Table 2 | Significant correlations between brain glucose consumption and the total recall score for the recent period (P4).

Neuroanatomical region	MNI coordinates (mm)			*k*	*Z*
	x	*y*	*z*		
P4 (INCLUDING THE TWO EVENTS)					
Left precuneus	−2	−54	22	109	3.98
Right precuneus	2	−56	22	52	3.71
Left calcarine region	−10	−102	−6	74	3.66
Left angular gyrus	−52	−60	40	125	3.45
Left middle temporal gyrus	−52	−66	14	33	3.32
Right middle temporal gyrus	42	−56	14	30	3.41
P4: "YESTERDAY" EVENTS					
Right supramarginal gyrus	60	−14	28	56	3.67
Right lingual gyrus	18	−86	−14	40	3.61
Right precuneus	2	−56	20	34	3.61
Left inferior frontal gyrus	−56	20	6	18	3.54
Left calcarine region	−12	−104	−4	10	3.35
Right middle temporal gyrus	52	−66	6	27	3.29
Right inferior temporal gyrus	46	−38	−18	14	3.88
P4: "TODAY" EVENTS					
No significant correlation					

k = cluster size > 10 voxels; correlations are reported at p < 0.001 (uncorrected).

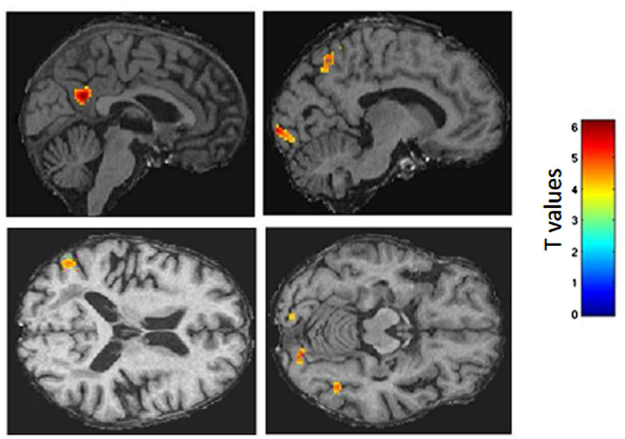


FIGURE 5 | Correlations between resting-state brain glucose consumption and autobiographical memory for recent events. Positive correlations are shown as colored voxels superimposed on sagittal sections of an individual AD patient's MRI normalized on the Montreal Neurological Institute (MNI) template ($p < 0.001$, uncorrected). The two sagittal sections (top) depict correlation with metabolism of the precuneus, calcarine region, and angular gyrus. The two axial sections (bottom) illustrate correlations with middle temporal gyri.

Compared to healthy controls, recall of autobiographical events was impaired in AD for all periods, excepted for the reminiscence bump period (P1). In addition, in AD patients, recall of very recent events (P4) was relatively better than for the periods covering the last 2 years and the last month (P2 and P3) and comparable to performance obtained for P1. Using resting-state PET imaging, we also revealed the brain areas subserving the retrieval of recent events in AD. Finally, we reported, for the first time, a correlation between the amount of slow-wave sleep and previous-day memory suggesting that the ability to consolidate episodic autobiographical memories is associated with sleep integrity.

The analysis of the total recall score revealed a temporally graded autobiographical amnesia in-line with previous reports (Kopelman, 1992; Nestor et al., 2002; Piolino et al., 2003; Hou et al., 2005). AD patients still exhibited a reminiscence bump, contrasting with a significant impairment for periods corresponding to the preclinical stages of their disease (the last 2 years). Furthermore, recall performance for the very recent past was comparable to that observed for the remote past, indicating that patients are still able to retain new personal specific information, provided the experienced events are relatively outstanding and different from typical daily events. Indeed, in the present study, patients had to recall an event that was new for them, coming to a different hospital than the one they used to visit for a sleep recording. However, when considering strictly episodic memories, patients were impaired for all periods, especially for the last month period (P3), confirming their altered capacity to recollect rich specific and unique personal episodes as reported in other studies conducted in Mild Cognitive Impairment (Tramoni et al., 2012) and in AD patients (Eustache et al., 2004; Martinelli et al., 2013b). The comparison of older adults and AD patients suggest that the content of autobiographical memories integrates more semantic, general information, and only few episodic details, as previously stated by Meulenbroek et al. (2010).

Recollective experience was also disrupted in AD patients as attested by the significant decrease in the number of Remember responses – justified or not-, fitting nicely with other studies (Piolino et al., 2003; Rauchs et al., 2007; Irish et al., 2010, 2011; Tramoni et al., 2012). However, for recent and remote memories (P4 and P1), patients still have a feeling a mentally reliving the events as attested by the lack of significant group differences for Remember and justified Remember responses. Some old memories can remain very vivid, even in AD patients, because they are particularly important for the subject's identity or are emotionally laden. For the very recent past, in this study, patients experienced events that were different from their everyday life, and therefore may be more resistant to forgetting. Our data indicate that they can have the feeling to relive these events, but cannot retrieve as much episodic details as healthy aged subjects. However, interestingly, patients provided significantly more Remember responses justified by phenomenological details for the recall of the events that occurred yesterday compared to those that occurred earlier during the day. This suggests that sleep, even if it is also disturbed in AD patients (Petit et al., 2004; Beaulieu-Bonneau and Hudon, 2009), can strengthen memory traces and reduce their sensitivity to forgetting. This point will be specifically discussed later.

Then, we looked at the brain areas subserving the recall of recent autobiographical memories in AD patients. To do so, we searched for correlations between autobiographical memory scores obtained for the period P4 and resting-state measures of brain glucose consumption. These analyses revealed that total

recall score for very recent events was related to the metabolism of posterior cortical areas, including the precuneus and retrosplenial cortex and the calcarine region, the angular gyrus and lateral temporal areas, mainly on the left side. These regions play a central role in the retrieval of episodic autobiographical memories (Svoboda et al., 2006; Cabeza and St Jacques, 2007; Martinelli et al., 2013a), even in older adults (Viard et al., 2007, 2010). The retrosplenial cortex is early and severely hypometabolic in the course of AD (Nestor et al., 2003) and its activity has been related to episodic memory loss in AD (Desgranges et al., 2002). Furthermore, several studies showed greater activation of this area for recent compared to remote autobiographical memories in healthy subjects (for review, Cabeza and St Jacques, 2007). Several accounts have been suggested to explain the more important role of this region, together with the calcarine area, in recent autobiographical memories, including the construction of generic visual representations, retrieval of personally familiar information, emotional processing, and vivid recollection (Cabeza and St Jacques, 2007).

Correlations were also found in lateral temporal areas. In healthy subjects, the left middle temporal gyrus may subtend the access to general information in-line with the constructivist model of autobiographical memory proposed by Conway (Conway and Pleydell-Pearce, 2000). Indeed, according to this model, memories are not stored as a perfect record of the original event, but are rather reconstructed from our autobiographical knowledge stores. Recollecting a specific autobiographical memory therefore requires to access first general information before retrieving more precise and specific elements. Viard et al. (2007) reported, in healthy aged subjects, an activation of lateral temporal areas only for the young adult period, suggesting that the reconstruction process occurs mainly for remote memories. In AD patients, however, the correlation observed between autobiographical memory scores for the recent past and left temporal activity suggest that they use this reconstructive process even when retrieving very recent events.

This pattern of correlation was observed for events that occurred yesterday and less for those that occurred the day of the examination. It suggests that these areas play a role in the retrieval of autobiographical memories that were already remodeled and reorganized within neural networks, in particular during sleep episodes, even if the consolidation process is not necessarily completed.

Whole brain regression analyses (but also region-of-interest analyses, data not shown) failed to reveal any significant correlation between memory scores and hippocampal activity, even at a more lenient statistical threshold. Given the fact that the hippocampus is one of the primary sites of AD pathology (Baron et al., 2001) and in light of a previous study conducted in our laboratory and revealing a correlation between hippocampal metabolism and autobiographical memory scores for the recent past (Eustache et al., 2004), this finding may appear unexpected. However, the recent period in Eustache et al. (2004) study covered the last 5 years and is therefore very different from the recent past explored here (yesterday and today), making the comparison between the two studies tricky. Another study using also the TEMPau task failed to reveal significant correlations between hippocampal metabolism and autobiographical memories experienced during the last 12 months, suggesting that the decline in autobiographical memory in early stages of AD may be due to a dysfunction of other brain regions within the autobiographical core brain network (Bastin et al., 2012), such as the posterior cingulate cortex, already associated to the decline of episodic memory performance (Chételat et al., 2003; Bastin et al., 2010), and the precuneus, involved in visual imagery (Fletcher et al., 1995). In our study, correlations were observed in some of these areas, notably the precuneus but also in the temporo-parieto-occipital junction. We mentioned above that the events experienced by patients during the period P4 were different from their everyday life, probably more emotional, and therefore may be more resistant to forgetting. Amygdala atrophy is prominent in early AD (Baron et al., 2001; Basso et al., 2006; Poulin et al., 2011). However, a beneficial effect of emotion on memory was reported in AD patients in some studies (e.g., Boller et al., 2002; Nieuwenhuis-Mark et al., 2009; Borg et al., 2011, see also Klein-Koerkamp et al., 2012 for review), albeit not consistently (Abrisqueta-Gomez et al., 2002; Kensinger et al., 2002, 2004). We surmise that the emotional valence of these recently experienced events together with the fact that they were particularly self-relevant and uncommon may have favored their encoding and consolidation.

The present study also aimed at investigating, for the first time, the impact of sleep on the quality of recall of recent autobiographical events. First, the two events of the very recent past period (P4), corresponding to what the patients did today and yesterday, were compared. This analysis disclosed better memory performance in AD patients, at least for the number of justified Remember responses, for events experienced the previous-day compared to those experienced the day of the assessment. The time elapsed between the encoding of memories and retrieval was much shorter for the same day memory (<12 h) than for the previous-day memory (about 24 h, with a night of sleep in-between). Thus, the difference observed between the two sub-periods could be due either to the fact that the retention interval was longer (but which is generally supposed to induce greater forgetting) or to a genuine effect of sleep. Further studies comparing memory retrieval after equal retention intervals filled with sleep (naps for instance) and wakefulness are further needed to disentangle this issue. However, we observed a positive correlation between the number of justified Remember responses and the percentage of time spent in slow-wave sleep, especially sleep stage 4. These results indicate that patients still exhibiting high amounts of slow-wave sleep have relatively better memory recollection that those whose sleep is disrupted. It also confirms that sleep disturbances in AD are not a secondary symptom of the disease, but can really worsen the cognitive performance, in-line with previous studies (Rauchs et al., 2008; Hot et al., 2011; Westerberg et al., 2012). The positive correlation with slow-wave sleep indicates that, despite an impairment of autobiographical memory especially for the period covering the last 2 years, consolidation of episodic autobiographical mnesic traces overnight is not totally disrupted at this stage of AD. These data are likewise reminiscent and extend those reported by Aly and Moscovitch (2010) in healthy older adults, showing that brain mechanisms supporting sleep-dependent memory consolidation may be preserved when the studied material engages one's interest.

In a previous study investigating, in young adults, the effect of sleep and sleep deprivation on consolidation of episodic memories

assessed by means of a word-list learning task, we showed that both slow-wave sleep and REM sleep are involved in the consolidation of rich, vivid episodic memories and that REM sleep favored preferentially the consolidation of spatial information and of details about the encoding context (Rauchs et al., 2004). This result was not replicated in the present study. Interestingly, sleep macrostructure in our group of AD patients only slightly differed compared to healthy aged controls, but both groups exhibited a marked decrease in the amount of slow-wave sleep compared to young adults. The positive correlation between justified Remember responses and time spent in slow-wave sleep suggest that the decrease in this sleep stage, classically observed in older adults, and even more in AD patients, would compromise the initial steps of memory consolidation and would prevent processes occurring normally during subsequent REM sleep to consolidate contextual details. Interestingly, Westerberg et al. (2012) also reported correlations between memory performance assessed using a word-pair recall task, and indices relative to slow-wave sleep (delta power in Non-REM sleep) in MCI patients.

To conclude, the present study shows that autobiographical memory is altered in AD patients across the entire lifespan, but with a relative preservation of memories that occurred during the very recent past. Retrieval of very recent events relies upon the functional integrity of the precuneus and retrosplenial cortex, the middle temporal cortex, and visual areas, reflecting at the same time access to general information, reconstruction, and visual imagery processes as well as recollection of specific details. Finally, we provide the first evidence of an association between the ability to recall recent autobiographical memories and preceding slow-wave sleep, highlighting the utmost importance of preserving sleep quality in older adults for optimal cognitive functioning.

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REFERENCES

Abrisqueta-Gomez, J., Bueno, O., Oliveira, M., and Bertolucci, P. (2002). Recognition memory for emotional pictures in Alzheimer's patients. *Acta Neurol. Scan.* 105, 51–54. doi:10.1034/j.1600-0404.2002.00035.x

Addis, D. R., and Tippett, L. J. (2004). Memory of myself: autobiographical memory and identity in Alzheimer's disease. *Memory* 12, 56–74. doi:10.1080/09658210244000423

Aly, M., and Moscovitch, M. (2010). The effects of sleep on episodic memory in older and younger adults. *Memory* 18, 327–334. doi:10.1080/09658211003601548

Baddeley, A. D., and Wilson, B. (1986). "Amnesia, autobiographical memory and confabulation," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 225–252.

Baron, J. C., Chételat, G., Desgranges, B., Perchey, G., Landeau, B., de La Sayette, V., et al. (2001). In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage* 14, 298–309. doi:10.1006/nimg.2001.0848

Basso, M., Yang, J., Warren, L., MacAvoy, M. G., Varma, P., Bronen, R. A., et al. (2006). Volumetry of amygdala and hippocampus and memory performance in Alzheimer's disease. *Psychiatry Res.* 146, 251–261. doi:10.1016/j.pscychresns.2006.01.007

Bastin, C., Feyers, D., Jedidi, H., Bahri, M. A., Degueldre, C., Lemaire, C., et al. (2012). Episodic autobiographical memory in amnestic mild cognitive impairment: what are the neural correlates? *Hum. Brain Mapp.* 34, 1811–1825. doi:10.1002/hbm.22032

Bastin, C., Kerrouche, N., Lekeu, F., Adam, S., Guillaume, B., Lemaire, C., et al. (2010). Controlled memory processes in questionable Alzheimer's disease: a view from neuroimaging research. *J. Alzheimer's Dis.* 20, 547–560. doi:10.3233/JAD-2010-1393

Beaulieu-Bonneau, S., and Hudon, C. (2009). Sleep disturbances in older adults with mild cognitive impairment. *Int. Psychogeriatr.* 21, 654–666. doi:10.1017/S1041610209009120

Boller, F., El Massioui, F., Devouche, E., Traykov, L., Pomati, S., and Starkstein, S. E. (2002). Processing emotional information in Alzheimer's disease: effects on memory performance and neurophysiological correlates. *Dement. Geriatr. Cogn. Disord.* 14, 104–112. doi:10.1159/000064932

Borg, C., Leroy, N., Favre, E., and Laurent, B. (2011). How emotional pictures influence visuospatial binding in short-term memory in ageing and Alzheimer's disease. *Brain Cogn.* 76, 20–25. doi:10.1016/j.bandc.2011.03.008

Born, J., Rasch, B., and Gais, S. (2006). Sleep to remember. *Neuroscientist* 12, 410–424. doi:10.1177/1073858406292647

Cabeza, R., and St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends Cogn. Sci.* 11, 219–227. doi:10.1016/j.tics.2007.02.005

Chételat, G., Desgranges, B., de La Sayette, V., Viader, F., Berkouk, K., Landeau, B., et al. (2003). Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 126, 1955–1967. doi:10.1093/brain/awg196

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–288. doi:10.1037/0033-295X.107.2.261

Conway, M. A., Pleydell-Pearce, C. W., Whitecross, S. E., and Sharpe, H. L. (2002). Brain imaging autobiographical memory. *Psychol. Learn. Motiv.* 41, 229–263. doi:10.1016/S0079-7421(02)80008-1

Desgranges, B., Baron, J.-C., Lalevée, C., Giffard, B., Viader, F., de La Sayette, V., et al. (2002). The neural substrates of episodic memory impairment in Alzheimer's disease as revealed by FDG-PET: relationship to degree of deterioration. *Brain* 125, 1116–1124. doi:10.1093/brain/awf097

Diekelmann, S., and Born, J. (2010). The memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126.

Eustache, F., Piolino, P., Giffard, B., Viader, F., de la Sayette, V., Baron, J.-C., et al. (2004). In the course of time: a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer's disease. *Brain* 127, 1549–1560. doi:10.1093/brain/awh166

Fletcher, P. C., Frith, C. D., Baker, S. C., Shallice, T., Frackowiak, R. S. J., and Dolan, R. J. (1995). The mind's eye: precuneus activation in memory-related imagery. *Neuroimage* 2, 195–200. doi:10.1006/nimg.1995.1025

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi:10.1016/0022-3956(75)90026-6

Gilboa, A., Ramirez, J., Köhler, S., Westmacott, R., Black, S. E., and Moscovitch, M. (2005). Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. *Hippocampus* 15, 535–550. doi:10.1002/hipo.20090

Greene, J. D., and Hodges, J. R. (1996). The fractionation of remote memory. evidence from a longitudinal study of dementia of Alzheimer type. *Brain* 119(Pt 1), 129–142. doi:10.1093/brain/119.1.129

Greene, J. D., Hodges, J. R., and Baddeley, A. D. (1995). Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia* 12, 1647–1670. doi:10.1016/0028-3932(95)00046-1

Harand, C., Bertran, F., Doidy, F., Guénolé, F., Desgranges, B., Eustache, F., et al. (2012). How aging affects sleep-dependent memory consolidation? *Front. Neurol.* 3:8. doi:10.3389/fneur.2012.00008

Hot, P., Rauchs, G., Bertran, F., Denise, P., Desgranges, B., Clochon, P., et al. (2011). Changes in sleep theta rhythm are related to episodic memory impairment in early Alzheimer's disease. *Biol. Psychol.* 87, 334–339. doi:10.1016/j.biopsycho.2011.04.002

Hou, C. E., Miller, B. L., and Kramer, J. H. (2005). Patterns of autobiographical memory loss in dementia. *Int. J. Geriatr. Psychiatry* 20, 809–815. doi:10.1002/gps.1361

Iber, C., Ancoli-Israel, S., Chesson, A., and Quan, S. F. (2007). *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* Westchester, IL: American Academy of Sleep Medicine.

Irish, M., Hornberger, M., Lah, S., Miller, L., Pengas, G., Nestor, P. J., et al. (2011). Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia* 49, 2694–2702. doi:10.1016/j.neuropsychologia.2011.05.017

Irish, M., Lawlor, B. A., O'Mara, S. M., and Coen, R. F. (2010). Exploring the recollective experience during autobiographical memory retrieval in amnestic mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 16, 546–555. doi:10.1017/S1355617710000172

Ivanoiu, A., Cooper, J. M., Shanks, M. F., and Venneri, A. (2004). Retrieval of episodic and semantic autobiographical memories in early Alzheimer's disease and semantic dementia. *Cortex* 40, 173–175. doi:10.1016/S0010-9452(08)70939-0

Kensinger, E. A., Anderson, A., Growdon, J. H., and Corkin, S. (2004). Effect of Alzheimer's disease on memory for verbal emotional information. *Neuropsychologia* 42, 791–800. doi:10.1016/j.neuropsychologia.2003.11.011

Kensinger, E. A., Brierley, B., Medford, N., Growdon, J. H., and Corkin, S. (2002). Effects of normal aging and Alzheimer's disease on emotional memory. *Emotion* 2, 118–134. doi:10.1037/1528-3542.2.2.118

Klein-Koerkamp, Y., Baciu, M., and Hot, P. (2012). Preserved and impaired emotional memory in Alzheimer's disease. *Front. Psychol.* 3:331. doi:10.3389/fpsyg.2012.00331

Kopelman, M. D. (1992). "The 'new' and the 'old': components of the anterograde and the retrograde memory loss in Korsakoff and Alzheimer patients," in *Neuropsychology of Memory*, eds L. R. Squire, and N. Butters (New York: Guilford Press), 130–146.

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.* 11, 724–744. doi:10.1080/01688638908400928

Leyhe, T., Müller, S., Milian, M., Eschweiler, G. W., and Saur, R. (2009). Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia* 47, 2464–2469. doi:10.1016/j.neuropsychologia.2009.04.018

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1441–1451. doi:10.1098/rstb.2001.0944

Mäntylä, T. (1993). Knowing but not remembering: adult age differences in recollective experience. *Mem. Cognit.* 21, 379–388. doi:10.3758/BF03208271

Martinelli, P., Sperduti, M., and Piolino, P. (2013a). Neural substrates of the self memory system: new insights from a meta-analysis. *Hum. Brain Mapp.* 34, 1515–1529. doi:10.1002/hbm.22008

Martinelli, P., Anssens, A., Sperduti, M., and Piolino, P. (2013b). The influence of normal aging and Alzheimer's disease in autobiographical memory highly related to the self. *Neuropsychology* 27, 69–78. doi:10.1037/a0030453

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34, 939–944. doi:10.1212/WNL.34.7.939

Meulenbroek, O., Rijpkema, M., Kessels, R. P., Rikkert, M. G., and Fernández, G. (2010). Autobiographical memory retrieval in patients with Alzheimer's disease. *Neuroimage* 53, 331–340. doi:10.1016/j.neuroimage.2010.05.082

Murphy, K. J., Troyer, A. K., Levine, B., and Moscovitch, M. (2008). Episodic, but not semantic, autobiographical memory is reduced in amnestic mild cognitive impairment. *Neuropsychologia* 46, 3116–3123. doi:10.1016/j

Nestor, P. J., Fryer, T. D., Ikeda, M., and Hodges, J. R. (2003). Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur. J. Neurosci.* 18, 2663–2667. doi:10.1046/j.1460-9568.2003.02999.x

Nestor, P. J., Graham, K. S., Bozeat, S., Simons, J. S., and Hodges, J. R. (2002). Memory consolidation and the hippocampus: further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. *Neuropsychologia* 40, 633–654. doi:10.1016/S0028-3932(01)00155-5

Nieuwenhuis-Mark, R. E., Schalk, K., and De Graaf, N. (2009). Free recall and learning of emotional word lists in very elderly people with and without dementia. *Am. J. Alzheimer Dis. Other. Demen.* 24, 155–162. doi:10.1177/1533317508330561

Nuwer, M. R., Comi, G., Emerson, R., Fuglsang-Frederiksen, A., Guerit, J. M., Hinrichs, H., et al. (1999). IFCN standards for digital recording of clinical EEG. The International Federation of Clinical Neurophysiology. *Electroencephalogr. Clin. Neurophysiol.* 52, 11–14.

Petit, D., Gagnon, J.-F., Fantini, M.-L., Ferini-Strambi, L., and Montplaisir, J. (2004). Sleep and quantitative EEG in neurodegenerative disorders. *J. Psychosom. Res.* 56, 487–496. doi:10.1016/j.jpsychores.2004.02.001

Philippi, N., Noblet, V., Botzung, A., Després, O., Renard, F., Sfikas, G., et al. (2012). MRI-based volumetry correlates of autobiographical memory in Alzheimer's disease. *PLoS ONE* 7:e46200. doi:10.1371/journal.pone.0046200

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevée, C., De la Sayette, V., et al. (2003). Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. *Brain* 126, 2203–2219. doi:10.1093/brain/awg222

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329. doi:10.1016/j.neuropsychologia.2009.01.020

Poulin, S. P., Dautoff, R., Morris, J. C., Barrett, L. F., and Dickerson, B. C. (2011). Amygdala atrophy is prominent in Alzheimer's disease and relates to symptom severity. *Psychiatry Res.* 194, 7–13. doi:10.1016/j.pscychresns.2011.06.014

Rauchs, G., Bertran, F., Guillery-Girard, B., Desgranges, B., Kerrouche, N., Denise, P., et al. (2004). Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. *Sleep* 27, 395–401.

Rauchs, G., Desgranges, B., Foret, J., and Eustache, F. (2005). The relationships between memory systems and sleep stages. *J. Sleep Res.* 14, 123–140. doi:10.1111/j.1365-2869.2005.00450.x

Rauchs, G., Piolino, P., Mézenge, F., Landeau, B., Lalevée, C., Pélerin, A., et al. (2007). Autonoetic consciousness in Alzheimer's disease: neuropsychological and PET findings using an episodic learning and recognition task. *Neurobiol. Aging* 28, 1410–1420. doi:10.1016/j.neurobiolaging.2006.06.005

Rauchs, G., Schabus, M., Parapatics, S., Bertran, F., Clochon, P., Hot, P., et al. (2008). Is there a link between sleep changes and memory in Alzheimer's disease? *Neuroreport* 19, 1159–1162. doi:10.1097/WNR.0b013e32830867c4

Rubin, D. C., Wetzler, S. E., and Nebes, R. D. (1986). "Autobiographical memory across the lifespan," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 202–221.

Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208. doi:10.1016/j.neuropsychologia.2006.05.023

Tramoni, E., Felician, O., Koric, L., Balzamo, M., Joubert, S., and Ceccaldi, M. (2012). Alteration of autobiographical memory in amnestic mild cognitive impairment. *Cortex* 48, 1310–1319. doi:10.1016/j.cortex.2011.09.002

Tulving, E. (1985). How many memory systems are there? *Am. Psychol.* 40, 385–398. doi:10.1037/0003-066X.40.4.385

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., and Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc. Natl. Acad. Sci. U.S.A.* 91, 2016–2020. doi:10.1073/pnas.91.6.2016

Tulving, E., Schacter, D. L., McLachlan, D. R., and Moscovitch, M. (1988). Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. *Brain Cogn.* 8, 3–20. doi:10.1016/0278-2626(88)90035-8

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289. doi:10.1006/nimg.2001.0978

Viard, A., Lebreton, K., Chételat, G., Desgranges, B., Landeau, B., Young, A., et al. (2010). Patterns of hippocampal-neocortical interactions in the retrieval of episodic autobiographical memories across the entire life-span of aged adults. *Hippocampus* 20, 153–165. doi:10.1002/hipo.20601

Viard, A., Piolino, P., Desgranges, B., Chételat, G., Lebreton, K., Landeau, B., et al. (2007). Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: an fMRI study. *Cereb. Cortex* 17, 2453–2467. doi:10.1093/cercor/bhl153

Westerberg, C. E., Mander, B. A., Florczak, S. M., Weintraub, S., Mesulam, M. M., Zee, P. C., et al. (2012). Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 18, 490–500. doi:10.1017/S135561771200001X

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Episodic memories and their relevance for psychoactive drug use and addiction

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The majority of adult people in western societies regularly consume psychoactive drugs. While this consumption is integrated in everyday life activities and controlled in most consumers, it may escalate and result in drug addiction. Non-addicted drug use requires the systematic establishment of highly organized behaviors, such as drug-seeking and -taking. While a significant role for classical and instrumental learning processes is well established in drug use and abuse, declarative drug memories have largely been neglected in research. Episodic memories are an important part of the declarative memories. Here a role of *episodic drug memories* in the establishment of non-addicted drug use and its transition to addiction is suggested. In relation to psychoactive drug consumption, episodic drug memories are formed when a person prepares for consumption, when the drug is consumed and, most important, when acute effects, withdrawal, craving, and relapse are experienced. Episodic drug memories are one-trial memories with emotional components that can be much stronger than "normal" episodic memories. Their establishment coincides with drug-induced neuronal activation and plasticity. These memories may be highly extinction resistant and influence psychoactive drug consumption, in particular during initial establishment and at the transition to "drug instrumentalization." In that, understanding how addictive drugs interact with episodic memory circuits in the brain may provide crucial information for how drug use and addiction are established.

Keywords: episodic drug memory, experimental consumption, drug instrumentalization, addiction

INTRODUCTION

> *"I smoked my first cigarette when I was 12 years old – behind the house, together with a few friends and some older guys who had provided it for trying. It was incredibly cool, not allowed of course, and it tasted awful. Despite persistent peer pressure, the memory of this one event still accompanies me until present day. It forms part of my personality and prevents me from trying cigarettes again. My first experience with alcohol a little later at the retirement party of my much beloved grand dad was quite bad as well. I felt sick and abstained from any countable consumption of alcohol for a few years. However, when I was a student I felt forced to social drinking which I tentatively did. At one occasion, however, I learned from rather unexpected feedback that my constitutively restricted social skills were tremendously enhanced after a few glasses of wine. This one episode, again vividly remembered to the present day, has shaped my drug consumption behaviour into another direction. After establishing a working dose window, I can now "instrumentalize" a controlled consumption for just this one purpose: "socializing on demand."*
>
> *(personal communication)*

These admittedly very personal example may illustrate that the availability of a psychoactive drug may lead to very different behavioral patterns in the long run after having established episodic memory of the first (few) drug consumption episodes. But do episodic memories just orchestrate other, more important learning processes at consciously accessible level or do they play a causal role in the establishment of regular drug consumption and addiction?

Psychoactive drugs are chemical compounds which influence our subjective perception and/or our behavior. Human beings consume psychoactive drugs voluntarily (Abel, 1980; Waldorf et al., 1991; Heath, 2000; Amendt, 2003). The consumption may range from a one-trial experience, after which the consummatory behavior is never repeated up to a stage of drug addiction when virtually all behavioral activity is directed toward the consumption of one or more psychoactive drugs. What starts with a single episode, remembered as an episodic memory, may finally control the complete behavioral repertoire of an individual.

Drug addiction is a now regarded a major psychiatric disorder which carries a considerable burden for individuals and their social environment (American Psychiatric Association, 1994). Much like other psychiatric disorders it compromises life quality of affected individuals and their families and has profound economic consequences. There is still no effective treatment available which may reverse the rather complex set of behaviors regarded as addiction, to a condition of either controlled drug use or abstinence. Understanding how drug addiction develops is, therefore, a major quest for behavioral neuroscience and psychiatry. While early views on addiction development were based on the action of psychoactive drugs as pharmacological reinforcers (Koob, 1992; Wise, 1994, 2002; Koob et al., 1998) and addiction as an aberrant learning mediated by the reinforcement system (Di Chiara, 1995), more recent views have acknowledged the role of various memory systems in the establishment of drug use and addiction (Nestler, 2002; Kelley, 2004; Hyman et al., 2006). A recent analysis suggests that

virtually all memory systems that humans are capable of might contribute to addiction development (Müller and Schumann, 2011a).

Importantly, not every individual who tries a psychoactive drug and establishes an episodic memory of the subsequent consummatory occasion with its aftermath becomes addicted to the drug. Inter-individual differences based on genetic (Stacey et al., 2009, 2012; Schumann et al., 2011; Easton et al., 2013a) and developmental factors (Campbell et al., 2009; Dong et al., 2011), accentuated personality traits (Piazza et al., 1989; Belin et al., 2008), or comorbid psychiatric disorders (Robbins and Everitt, 1999) appear to predispose individuals differently to the risk of fast establishment of drug consumption and/or the transition from controlled to compulsive drug use. However, most regular consumers of psychoactive drugs do never become addicts. Large consumer surveys in the US (SAMHSA, 2011) and Europe (EMCDDA, 2012) reveal that the majority of the regular consumers of legal drugs like alcohol or illicit drugs like cannabis or cocaine may exert a lifelong control over their consumption (Ahmed, 2010; Müller and Schumann, 2011a). However, a significant minority of those humans and animals, who have established drug-seeking and consumption behaviors lose control and develop a compulsive pattern of consumption (Gawin, 1991; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004).

While it is currently under debate whether the controlled use of psychoactive drugs might under certain circumstances have beneficial effects for behavioral performance, the achievement of life goals, or wellbeing (Lende and Smith, 2002; Lende et al., 2007; Hagen et al., 2009; Müller and Schumann, 2011a,b), it has to be acknowledged that the behavior of psychoactive drug consumption is established by the majority of humans in the western world and forms a rather stable trait. Since neither humans nor drug consuming animals are developmentally determined to automatically establish drug consumption, it may be assumed that the stability of this trait over generations is based on the capability to learn it by social learning or *de novo* (Müller and Schumann, 2011a). The ability to modify food consumption according to non-nutritional needs may be seen as the phylogenetic origin of psychoactive drug consumption. This capability is already present in various animal species (Rodriguez and Wrangham, 1993; Lozano, 1998; Huffman, 2003). The learning of consummatory behaviors may then involve either a learning by trial-and-error (e.g., for newly emerging substances; Hassan et al., 2013), or by cultural inheritance/learning (Dean et al., 2012). Importantly, any way to acquire drug consumption related behaviors involves learning and memory processes. The high persistence of the behavior after long periods of abstinence suggests high stability and extinction resistance of related memories.

The goal of this paper was to review the role of episodic memories in non-addicted psychoactive drug use and in drug addiction. While there is no such role acknowledged yet, this is to my knowledge the first attempt to make a case for episodic drug memories and their function. I will first consider the role of learning and memories in the establishment of drug use behaviors and review the history of drug- and addiction memory concepts. Then a recently suggested concept of drug memories is discussed which includes for the first time also episodic drug memories. An attempt is made to further refine a potential definition of episodic drug memories. It is discussed when in the time course of establishing drug use and abuse behaviors, they might play a role. Finally I review some of the neuropharmacological evidence for brain processes, potentially related to episodic drug memories. This discussion is meant to introduce episodic drug memories into the frame of relevant memory systems for drug use and addiction. As such it may not be complete and cannot deliver final conclusions, but should be understood as a first suggestion for subsequent debate.

DRUG USE REQUIRES MEMORIES

According to current diagnostic manuals, drug addiction is diagnosed by the incidence of a number of rather complex behaviors which involve, e.g., mental occupation with the drug, active seeking of the drug, and active drug consumption. Most important, it also involves compulsive drug use and relapse long after the drug has left the organism and even long after compensatory processes in the brain have subsided. Thus, it was suggested that drug addiction may be based on memory formation and voluntary and involuntary retrieval.

Although still poorly defined in psychological terms, the concept of a *drug-* or *addiction memory* is not new (Boening, 2001). Mello (1972) introduced the term "memory of addiction" in a discussion of addiction-related behaviors. However, the dominating concept of drug action at that time and later on assumed that the reinforcing effects of psychoactive drugs were mostly dissociated from their interaction with memory systems (White and Milner, 1992). Nevertheless, several lines of evidence suggested important interactions of psychoactive drugs with memory systems. It was shown in animals and humans that drug-associated cues can work as a classically conditioned stimulus and induce either drug-related effects or withdrawal symptoms (Wikler and Pescor, 1967; Siegel, 1975; O'Brien et al., 1977; Siegel et al., 1982). The conditioned withdrawal symptoms, which can be ameliorated almost immediately by new drug consumption, were assumed to contribute significantly to the continuation of the drug use (Siegel, 1988; O'Brien et al., 1998; but, see Drummond et al., 1990). Another line of evidence showed that psychoactive drugs applied post trial can also enhance memory for non-drug-related behaviors (Huston et al., 1974, 1977), thus indicating that drugs do not just shape memories to acute drug-effects, but also of preceding events and behaviors. White (1996), when summarizing the evidence, suggested that the reinforcing effects of addictive drugs may at least in part be brought about by their interaction with multiple memory systems of the brain. He suggested three general types of memory that are influenced independently by psychoactive drugs. These systems would be involved in conditioned incentive learning, declarative learning, and habit or stimulus-response learning. Conditioned incentive learning described the learning of stimulus-incentive associations, after which a neutral cue would become a conditioned reward that is able to elicit conditioned approach behavior (Squire et al., 1993; Milner et al., 1998). Major brain structures mediating the influence of psychoactive drugs on conditioned incentive learning are the amygdala, the nucleus accumbens, and the tegmental pedunculopontine nucleus (White, 1996). Declarative learning describes the

learning of relationships among cues which can be neutral in their consequences, also known as stimulus–stimulus learning (Squire et al., 1993; Milner et al., 1998). In contrast to non-declarative memories, the content of declarative memories should be consciously accessible (Squire et al., 1993; Milner et al., 1998). In terms of addiction memory, it contains information on the relationships among external cues and events relevant for drug taking (White, 1996). Brain structures that are involved are the hippocampus network and the neocortex (Milner et al., 1998; Bast, 2007). Habit learning described the learning of stimulus-response associations, which are strengthened by the occurrence of reinforcement. The neural correlate for habit learning is the caudate-putamen (Knowlton et al., 1996; Milner et al., 1998). An important role of habit learning for drug addiction was early recognized in particular for drug self-administration behavior (White, 1989, 1996). This view received important support from more recent studies demonstrating not only the neuroanatomical preconditions (Haber et al., 2000), but also their functional relevance for a transfer of information between stimulus-outcome learning and stimulus-response learning systems (Porrino et al., 2004; Belin and Everitt, 2008). White (1996) argued that the addictive properties of drugs have multiple causes based on their multiple independent interactions with those memory systems which store different aspects of the drug experience and of drug taking behaviors. Another classification of addiction memories was proposed by Heyne et al. (2000). They suggested distinguishing at least three different memory types in relation to drug consumption: a memory of drug-effects, a memory of drug use, and a memory of addiction (Heyne et al., 2000; Boening, 2001).

A more recent view considered the hypothesis that drug addiction may be understood in terms of recruitment of neural systems that normally mediate learning and memory (Robbins et al., 2008). Thereby, drugs are assumed to always work as unconditioned reinforcers which support emotional learning, encompassing Pavlovian as well as instrumental conditioning. The amygdala, nucleus accumbens, and orbitofrontal cortex play important roles in the acquisition and retrieval of emotional memories related to the drug (Kilts et al., 2001; Everitt et al., 2007). For the procedural (habit) learning system, a cascading loop transfer of cue-controlled drug-related behavior from the ventral to the dorsal striatum was suggested (Robbins et al., 2008). It was concluded that "addiction is a product of aberrant associative learning" which might also involve other pathological changes in behavior. A significant part of its aberrant nature might be its compulsive impact on drug-seeking and -taking behavior, which was suggested to be mediated by a loss of prefrontal cortex control over drug-related habits in the dorsal striatum (Belin et al., 2009). Although this model acknowledges important roles of memory circuits in drug addiction, the view on potential types of memories involved in drug use remains somewhat incomplete and limited to the concept of addiction. It should be noted that there appeared a conceptual gap between the concepts of addiction and the supportive literature on brain mechanisms. Virtually all evidence derived from the host of animal studies did actually not measure the syndrome of addiction, but only single drug-associated behaviors which were not established up to the level of compulsiveness (but, see Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In that, conclusions on brain mechanisms might predominantly apply to non-addicted drug use and only serve as a starting point for neuronal adaptations related to addiction.

To allow for a more focused research in the subtypes of a drug memory, a nomenclature for different subtypes of memories was recently suggested by Müller and Schumann (2011a). Research in the neuronal mechanisms of non-drug memories has shown that there are different memories with distinct neuronal mechanism (Eichenbaum, 1997; Milner et al., 1998; McGaugh, 2000). It was suggested that a similar differentiation might also help to segregate single types of drug-related memories and elucidate crucial neuronal mechanism. Accordingly, the drug memory nomenclature was expanded to the types of memories originally identified for non-drug-related experiences (Squire et al., 1993; Milner et al., 1998).

For drug memory it is suggested to distinguish two major categories: a *declarative drug memory* and a *non-declarative drug memory* (**Figure 1**). The declarative drug memory contains information that is consciously accessible, i.e., it can be reported verbally by humans. The declarative drug memory should comprise a *semantic memory* for drug facts and one for *drug episodes*. The semantic memory for drugs contains all impersonal facts, rules, and concepts involving drugs, e.g., their names, where they come from, recommended doses, what others report about its effects, and what the rules of their consumption are (Müller and Schumann, 2011a). The establishment of this type of drug memory usually starts before a person is engaged in the first episode of consumption by learning facts from others about the drug (Miller et al., 1990; Leigh and Stacy, 2004). By that way an early semantic drug memory shapes the first expectations of drug-effects, which is then constantly adapted after actual consumption started (Kidorf et al., 1995). It was suggested to conceptualize the expectation of drug-effects (Leigh, 1989; Del Boca et al., 2002) as a retrieval process from different types of memories (Goldman et al., 1991). Also in experienced users, it was shown that the expectation of the drug-effects can still shape the physiological effects of the drug as well as its subjective perception (Volkow et al., 2003, 2006), and thus, influence the establishment of episodic drug memories.

The *episodic drug memory* comprises the memories of all personally experienced episodes with the drug. It is an autobiographical memory of the "What," "Where," and "When" of the personal drug encounters. It involves an "autonoetic awareness" of single drug experiences in the continuity of ones subjectively apprehended time. It involves a remembering of the drug episodes as well as "thinking about" the drug when planning for future behavior (Tulving, 2001; Dere et al., 2006, 2008). This may include automatically formed memories of subjectively experienced acute drug-effects, e.g., the mental states the drug induced. The episodic drug memory also comprises aversive withdrawal episodes and periods during subsequent abstinence. These episodes are either characterized by the feeling of drug craving or mental preoccupation with the drug. Clearly, relapse episodes also have episodic memory components. The episodic drug memory system can also contain memories of what was done during a particular drug-induced mental state, and even what effects it had in terms of the environmental feedback (Boening, 2001). In accordance with Tulving's definition (Tulving, 2002), also episodic

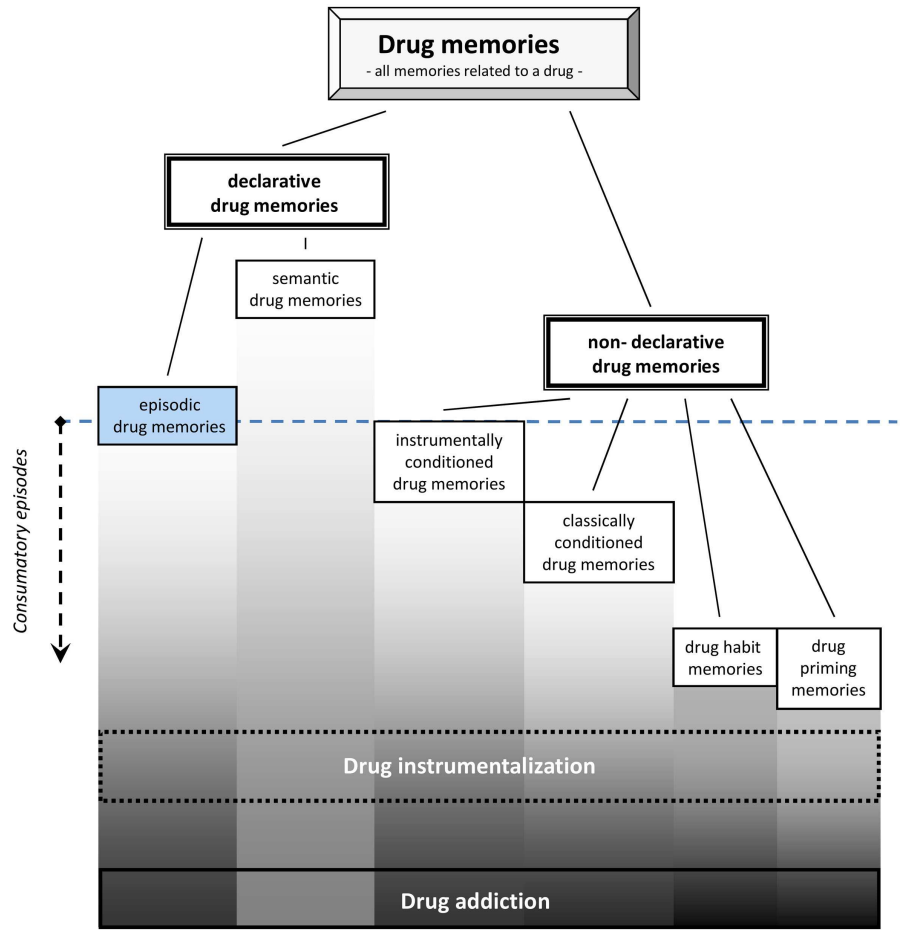


FIGURE 1 | Episodic and other drug memory systems as they are established during drug consumption. Note that semantic drug memories may already establish before first drug consumption, while episodic drug memories require only single consumption episode [modified from Müller and Schumann (2011a)].

drug memories involve the ability for "mental time travel" and "conscious recollection."

While the experience of "euphoria" or a "high" is often the sought after mental state, it is not the only one occurring on the time scale of a drug consumption episode. A single drug episode may better be considered as a sequence of several distinct mental states. This can be measured as the discriminative stimulus properties of a drug. The discriminative stimulus properties are directly reflecting the mental state induced by a psychoactive drug (Overton, 1968; Stolerman, 1992). As such, this type of memory appears to be crucial for "drug instrumentalization" (Müller and Schumann, 2011a,b). An episodic drug memory requires only a single learning trial, but may be extinction resistant up to a whole life span. Its retrieval may trigger psychoactive drug-seeking and taking, but also passive avoidance of the drug (Eissenberg and Balster, 2000; Miller, 2001).

The *non-declarative drug memory*, in contrast, is not consciously accessible and can only be inferred from behavioral changes in animals and humans. The non-declarative drug memories contain engrams of the classically conditioned drug memory, instrumentally conditioned drug memory, habit memory, procedural drug memories, and drug priming memories.

Classically conditioned drug memories may contain all drug-effects that refer to the process of Pavlovian conditioning (Bouton and Moody, 2004). These may include, e.g., the sensitization of the acute drug-effects (Kalivas et al., 1993; Vanderschuren and Kalivas, 2000), drug tolerance, conditioned locomotor activity, conditioned emotional and physiological responses (Foltin and Haney, 2000), conditioned place preference (Bardo and Bevins, 2000; Tzschentke, 2007), and conditioned withdrawal effects (Goldberg, 1975; Siegel, 1988; O'Brien et al., 1998).

Instrumentally conditioned drug memories comprise engrams established by instrumental conditioning. Major behaviors induced by the retrieval of those engrams are drug-seeking behaviors and drug self-administration (Spealman and Goldberg, 1978; Richardson and Roberts, 1996). These memories also include drug-cues which are rewarding by themself, as shown in conditioned place preference (Huston et al., 2013), or which can

re-instate drug-seeking and drug self-administration behavior (de Wit and Stewart, 1981; Shaham et al., 2003).

Drug habit memories refer to instrumental behavior that is no longer goal directed, but stimulus controlled, i.e., a behavioral response that is triggered by a cue, but independent from its behavioral consequences (Everitt and Robbins, 2005). This type of memory is not only important for the transition from controlled to compulsive drug use and addiction (Porrino et al., 2004; Belin and Everitt, 2008), but may already in non-addicted drug users play a role in stimulus driven drug instrumentalization.

Procedural drug memories comprise all memories for skills involved in handling a drug. This may range from its production (e.g., cooking up heroin; rolling a joint with marijuana) to the actual way of self-administration (e.g., snorting cocaine; setting a needle for an i.v. heroin injection).

The *Drug priming memories* refer to those engrams whose activation by a small amounts of the drug, which would not induce major subjective and behavioral effects in drug naïve individuals, may in an experienced user induce drug-related behavior (e.g., re-instate drug-seeking, conditioned place preference, or self-administration) and subjective effects (**Figure 1**).

It was recently suggested that the majority of non-addicted humans, who consume psychoactive drugs as an integral part of their lives (O'Malley and Johnston, 2002; Skogen et al., 2009) take drugs because the subsequent effects can be used for their personal goals in a systematic way. Evidence reviewed by Müller and Schumann (2011a,b) suggests that psychoactive drugs can be "*instrumentalized*," i.e., used like an instrument. Thereby, "*drug instrumentalization*" was defined as a two-step behavioral complex of two interconnected processes: (a) the seeking and consumption of a psychoactive drug in order to change the present mental state into a previously learned mental state, which then allows for (b) a better performance of other, previously established behaviors and a better goal achievement by these behaviors. It was suggested that drug instrumentalization requires the interplay of various, if not all, types of drug memories which need to be established during different stages of experimental consumption (Müller and Schumann, 2011a).

It was suggested that drug-related behaviors, including self-administration, can be learned and maintained in several ways, which may also involve contributions of several memory systems to what appears as one behavioral output, but may in fact contain many different sequences (White, 1996). Externally induced or spontaneous retrieval from certain types of the drug memories allows for a systematic instrumentalization of the drug's psychotropic effects. Thereby, episodic and instrumentally conditioned drug memories may be considered as the most important memories for drug instrumentalization.

It should be noted that the occurrence of these memories does not automatically implicate a transition to addition. In fact, most people with drug experience are able to manage drug use and instrumentalization in order to gain a fitness benefit within socially approved limits during their entire life. A drug memory is, therefore, not an indicator for drug addiction. Learning and memory research in relation to psychoactive drugs aimed mostly at defining the memory in relation to addiction as an *addiction memory*, although animal models depicted mostly non-addicted consumption; Olmstead, 2006; Sanchis-Segura and Spanagel, 2006). In line with White (1996) and Heyne et al. (2000), a distinction between *drug memory* and *addiction memory* is suggested, based on the degree of elaboration and the compulsive nature that the retrieval of memories has in addiction (**Figure 1**). In that, the drug memory should comprise all information about psychoactive drugs as defined above, whereas an addiction memory contains quantitatively more of this information with stronger engrams that are more powerful to suppress non-drug memories. Considering the compulsive nature of drug addiction, it cannot be ruled out that there will also be some sort of qualitative differences in the engrams and/or the retrieval of the memories.

THE SPECIFIC NATURE OF EPISODIC DRUG MEMORIES

Episodic memories are major constituents of an individual personality. The encoding and later retrieval of episodes and experiences shapes individual biographies and makes memories accessible for individuals later in live. This also comprises the psychoactive drug biography, i.e., the consumer history of an individual. In that single consummatory episodes may be the substrate of what is remembered in an episodic drug memory. In contrast to non-drug episodes, there are some specific properties to the "What," "Where," and "When" criteria of episodic drug memories. The classical concept of episodic memory refers to three external dimensions; the "What" refers to an event or series of external stimuli, the "Where" is an external place, and the "When" describes subjectively anchored time referenced to an individual's life (Tulving, 2001). Episodic drug memories may expand all three components by a subjective and social cognitive component:

What: the "*What*" may be best defined as the drug-effect on the mental state of an individual, in fact being a series of introspectively perceived mental state changes. This usually happens parallel to perceived changes in autonomous system activity (e.g., sickness after a heroin injection) and is influenced by external events (e.g., dance music during an ecstasy episode). One drug episode may involve several different mental states. As, for example, an alcohol episode may involve the sequence of "sobriety – slight disinhibition – emotional high – sedation – hangover with headaches."

Where: drug-effects do not only depend on the dose of a particular substance but also on the *set* and *setting* of the individual (Zinberg, 1984). As such the "Where" component may comprise not only a spatial environment, but the overall setting of a consummatory episode. Thereby the *setting* involves social parameters such as peers present and psychological factors like peer group pressure. The *setting* also involves expectations on the subjective effects of the drug that is about to be consumed, and on emotional arousal derived there from Volkow et al. (2003, 2006).

When: the "When" refers to a temporal localization of an event in the individuals own biography. However, this may also include the *set* of a person at this time point, i.e., the physical constitution and mental state a person was in at the moment of drug-seeking and consumption.

The earliest episodic drug memories of an individual are established upon the first encounter with a drug when the experimental consumption has no other goal than to experience the mental state change and other physiological effects induced by a psychoactive drug. In its simplest form, episodic drug memories may be a compound percept of a time in personal history with a particular mental state (When), a spatial location with all present social influences (Where), and the mental (and physiological) state change that the drug induced (What). This may for instance be the memory of an episode when a slightly anxious and aroused adolescent person tries alcohol for the first time in a group of friends following social pressure to do so and experiencing a burning taste with some dizziness afterward.

Once drug consumption has been initially established, but is not at the level of a habit yet, there is another important occasion when episodic drug memories come into play: the establishment of "drug instrumentalization." It was argued before that during experimental consumption, humans and animals do not only learn the set and setting of drug-effects, but also the instrumentalization of a drug (Müller and Schumann, 2011b). Thus, it is postulated that a particular type of episodic drug memories will include additional components related to the drug's instrumentalization, such as:

What: the beneficial effects on non-drug-related behavior by a drug-induced change of mental state.

Where: a place or situation where both are available/possible, a particular psychoactive drug and a chance to perform a goal-directed instrumental behavior.

When: a given situation, where the present mental state of an individual appears to be a suboptimal state for a desired goal-directed behavior, so that a mental state change is desirable.

The components of a drug-instrumentalization episodic memory may for example include engrams of a pub with alcohol and potential sex partners available as chance for rewarded behavior (Where). It may include the memory of a date and time but also of a stressed and tired mental state with the wish to change this to a relaxed and slightly disinhibited mental state (When). Finally it may comprise the memory of having a few drinks that changed the initial to the desired mental state with a subsequent successful social interaction and securing a partner for life (What).

Evidence for these types of compound drug memories may be derived from numerous verbal reports of drug users that are able to consciously retrieve rather complex "What-Where-When" information of their drug-instrumentalization episodes (Waldorf et al., 1991; Heath, 2000; Boys et al., 2001; Boys and Marsden, 2003; Boyd et al., 2006; Frederiksen et al., 2012). One may argue that these are conscious self-analyses of one's own instrumentally conditioned behavior. However, it is well known that instrumental conditioning, in particular of complex behavioral sequences, requires numerous learning trials. Many drug users, however, can report single events as crucial and sometimes life-changing episodes. This might favor the view that there are persistent one-trial drug memories which are very complex and extinction resistant.

While there is no doubt on whether there are episodic drug memories, it is not entirely clear which causal role they might play in the course of establishing drug consumption, instrumentalization and, possibly, addiction. Here it is suggested that episodic drug memories play important roles at least at two different stages in the etiology of drug use: during the initiation of consumption and at the transition to drug instrumentalization.

Drug use behaviors start with experimental consumption usually during adolescence (Sher et al., 2005) with a rather undifferentiated consumption (Spear, 2000; Kuntsche et al., 2005). Experimental consumption, in contrast to instrumentalization and compulsive consumption, refers to a consummatory behavior of which the consequences are initially unknown to the individual. The introduction to the drug in appropriate settings is usually done by older and/or more experienced members of the peer group (e.g., Friedman et al., 1985; Eissenberg and Balster, 2000). However, given inter-individual differences in drug pharmacokinetics and -dynamics, in personality, and in life circumstances, each person has to customize the drug use. It should be noted that although there are expectancies of the drug-effects in drug naïve consumers (Miller et al., 1990), the individual response profile after first consumption is often unpredictable (e.g., Waskow et al., 1970; Jones, 1971). Importantly, during experimental consumption not only the effects of a drug are explored at usually different doses and settings (Patrick and Maggs, 2008). At the same time it is also experimented with how the drug-effects on mental states can be "used" in relation to different settings (Zinberg, 1984; Simons et al., 2000). Thereby numerous episodic drug memories are formed which guide later parameters of consumption. Evidence for a systematic knowledge about drugs and drug-effects is provided by the elaborate expectancies that people develop toward the drug-effects before and during consumption (e.g., Brown et al., 1980; Brown, 1985; Gustafson, 1991; Peele and Brodsky, 2000). As such, an individual dose titration can be the consequence of a series of episodes with either too low or too high doses and perceived subjective and behavioral consequences.

The other important time when episodic memories guide future consumption is the establishment of drug instrumentalization. This occurs usually not after first consumption, but requires already some experience with the drug including the knowledge of an individual dose-effect relationship. The learning of drug-instrumentalization involves an extension of the episodic drug memory components in terms of the preconditions and consequences of behavior. However, it can still be a one-trial experience by which future drug use is shaped. Several reports from drug users show that the perceived and reported "usefulness" of the drug-effects was found to predict future use of the drugs (Boys et al., 1999; Boys and Marsden, 2003; Leigh and Stacy, 2004). For instance, a certain dose of alcohol can be a boring experience when consumed alone at home by a teenager, i.e., when no instrumentalization is possible, while the disinhibitory effects of the same dose may be found highly entertaining and rewarding at a party with peers and the opposite sex. In this case, an episodic drug memory is established which contributes to later drug instrumentalization. It can be retrieved at a future occasion to facilitate socializing and mating approaches.

It was argued that one pathway into addiction is by an attempted over-instrumentalization of drug-effects, e.g., under stressed conditions (Kippin, 2011; Müller and Schumann, 2011b). While episodic memories may contribute to it, important processes most likely involve classical and instrumental conditioning and habit learning (Everitt and Robbins, 2005). At present one cannot say if there is a role of episodic memories in the transition from regular drug use and instrumentalization to compulsive use and addiction.

ACUTE PHYSIOLOGICAL EFFECTS OF DRUGS IN MEMORY SYSTEMS OF THE BRAIN

One way to investigate the neuronal mechanisms of episodic drug memories may be to look at the first encounter with an addictive drug. At this time, no conditioned drug-effects are established, and no adaptive or neurotoxic drug-effects have occurred in the brain. In this section I look at those acute drug-effects which might serve or influence episodic drug memories in drug naïve individuals.

DOPAMINE AND SEROTONIN

Psychotropic drugs exert profound effects on extracellular neurotransmitter activity. A significant increase in dopaminergic (DA) activity was reported, which is particularly well documented in the mesolimbic system for alcohol (McBride et al., 2002; Tupala and Tiihonen, 2004; Spanagel, 2009), nicotine (Markou, 2008), cocaine (Di Chiara and Imperato, 1988; Johanson and Fischman, 1989; Müller et al., 2002), amphetamines (Seiden et al., 1993; Green et al., 2003; Müller et al., 2007a), opiates (Di Chiara and North, 1992; McBride et al., 1999), cannabis/marijuana (Ameri, 1999; Iversen, 2000), and caffeine (Cauli and Morelli, 2005). However, activation of DA activity was also described for, e.g., cocaine and amphetamine in the neocortex and the hippocampus and related cortical structures (Müller and Huston, 2007; Pum et al., 2007). There is now good evidence for a functional role of the DA effects in the mesolimbic system for the establishment of various addiction-related behaviors (Koob et al., 1998; Wise, 2002; Pierce and Kumaresan, 2006). The functional role in most memory-associated structures still has to be determined. Importantly, DA activation plays also an important functional role in various types of memory, such as working memory (Williams and Goldman-Rakic, 1995; Wang et al., 2004) and reward learning (Schultz, 2000; Willuhn et al., 2012). It may be speculated that a drug-induced DA activation is an early step in amplifying learning processes. Although DA is a central mechanism for addiction and learning and memory, it is by far not the only transmitter which is acutely activated. Various psychoactive drugs enhance also serotonergic activity (5-HT; Müller et al., 2004, 2007b, 2010). Animal studies showed that psychoactive drugs like cocaine and amphetamine induce strong 5-HT responses in several neocortical and hippocampus-associated regions (Müller et al., 2004, 2007b; Pum et al., 2007) which play important roles in components of the episodic memory (Aggleton and Brown, 1999; Dere et al., 2006, 2007).

Formation of an episodic memory depends on emotional valence of the perceived episode. The higher the emotional valence, the more likely it appears for the event to be remembered. High emotional impact is characterized by strong activation of emotion processing systems, such as serotonin responses in the amygdala for negative emotions (Rex et al., 1993; Pum et al., 2009) or dopamine responses in the nucleus accumbens for unexpected positive valence (Schultz, 2000; Willuhn et al., 2012). The neurochemical acute effects of psychoactive drugs in emotion processing brain areas usually exaggerate the activation by natural stimuli (Rueter et al., 1997; Müller et al., 2007a). This may result in a mock signal of emotional importance of the preceding events and behavior (Nesse and Berridge, 1997), but a very real episodic memory thereof.

ACETYLCHOLINE

The acetylcholinergic (ACh) system plays an important role in attentional and memory processes (Blokland, 1995; Sarter et al., 2005) and is crucially involved in consciousness (Perry et al., 1999; Müller et al., 2011; Woolf and Butcher, 2011) and episodic memory (Dere et al., 2007). Acute application of cocaine was shown to activate cholinergic interneurons in the nucleus accumbens (Witten et al., 2010). Several drugs have been shown to increase extracellular ACh levels after acute application, such as cocaine, amphetamine, morphine, alcohol, and nicotine. It was observed in the ventral striatum, caudate nucleus, cortex, and ventral tegmental area (VTA), but most pronounced in the hippocampus (Imperato et al., 1992, 1993a, 1996; Quirion et al., 1994; Zocchi and Pert, 1994; Summers and Giacobini, 1995; Henn et al., 1998; Consolo et al., 1999; Larsson et al., 2005). The later effect was suggested to be a potential base for drug-effects on declarative memories (Williams and Adinoff, 2008). The nicotine-induced ACh increase is mediated by local nicotinergic ACh receptors (Summers and Giacobini, 1995; Tani et al., 1998). It was shown that the psychostimulant-induced ACh increase was not mediated by direct interaction with muscarinergic or nicotinergic ACh receptors, but depends mainly on DA-induced D1 receptor activation (Imperato et al., 1992, 1993a,b; Consolo et al., 1999). While a crucial role of the ACh system in addiction-related behaviors which require instrumental and classical conditioning is now evident (Bardo, 1998; McBride et al., 1999; Williams and Adinoff, 2008), a functional role of acute drug-effects in the ACh system for episodic drug memories still needs to be investigated.

GLUTAMATE

An important finding was that major drugs of addiction, such as cocaine, amphetamine, morphine, ethanol, and nicotine can enhance synaptic plasticity at excitatory synapses in VTA DA neurons, as measured by the ratio of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)- and *N*-methyl-D-aspartate receptor (NMDA) dependent excitatory post-synaptic currents (EPSCs; Ungless et al., 2001; Saal et al., 2003; Faleiro et al., 2004). This plasticity is persistent for several days during which it may be the base for behavioral hypersensitivity (Borgland et al., 2004; Wanat and Bonci, 2008; Zweifel et al., 2008). Downstream mechanisms for this fast plasticity include protein synthesis, a reduced NMDA receptor function, and the active insertion of GluR2-lacking AMPA receptors, such as GluR1-containing AMPA receptors (Dong et al., 2004; Argilli et al., 2008; Mameli et al., 2011). GluR2-lacking AMPA receptors have a greater channel conductance and are Ca^{2+} permeable, which allows them

to trigger also Ca^{2+} dependent signaling cascades (Bowers et al., 2010). It should be noted, however, that none of the investigated drugs induces addiction after a single administration in humans or animals. However, there is some learning involved already after a single drug exposure, which may in animals include a one-trial conditioned place preference (Zweifel et al., 2008), and also the memory of the self-administration episode. As such, early synaptic plasticity after acute drug exposure may be an important substrate of one-trial episodic drug memory. Neurophysiological studies have so far focused mainly on DA neurons in the VTA. Given the omnipresence of neuroplasticity at glutamatergic synapses in the brain and the dopamine-independent effects of some addictive drugs (Pierce and Kumaresan, 2006), it would be important to investigate the potential of addictive drugs to cause this early plasticity also in other memory-related synapses.

INTRACELLULAR SIGNALING CASCADES

The concept of drug memory proofed to be useful when animal studies revealed that many of the molecular changes at cellular level, which occurred after single and chronic drug administration, were similar to those observed during normal learning. Drugs of addiction, for example, acutely increased the levels the second messenger, cyclic adenosine monophosphate (cAMP), and activated the protein kinase A – cAMP-response element binding protein (CREB) cascade, which regulates gene transcription and protein synthesis. This leads, among others, to changes in the expression of NMDA and AMPA glutamate receptors (Nestler and Aghajanian, 1997; Hyman and Malenka, 2001; Nestler, 2002; Hyman et al., 2006; Kauer and Malenka, 2007). In particular CREB-regulated gene transcription and protein synthesis are believed to be essential mechanisms for long lasting cellular and behavioral plasticity (Kandel and Pittenger, 1999; Kandel, 2001). Another important pathway activated by drugs of addiction involves the second messenger Ca^{2+}, calmodulin, and Ca^{2+}/Calmodulin-dependent-kinases. Activation of this pathway is essential for various types of learning (Giese et al., 1998; Irvine et al., 2006; Easton et al., 2013b) as well as for several drug-related behaviors (Licata and Pierce, 2003; Liu et al., 2006; Anderson et al., 2008; Bilbao et al., 2008; Easton et al., 2013a). A series of functional studies showed that antisense oligodeoxynucleotides for the immediate early gene, Zif268, in the basolateral amygdala could disrupt different memories for cocaine and heroin (Lee et al., 2005, 2006; Hellemans et al., 2006). Altogether, drugs of addiction were shown to be very efficient in activating gene transcription factors (Nestler, 2008) and cellular plasticity after only a single drug exposure for several days (Hyman et al., 2006; Ungless et al., 2010). Both are indicators of cellular processes underlying fast learning (Morris et al., 1986; Aggleton and Brown, 2005).

NEURONAL MORPHOLOGY

There is a growing physiological base for drug-related memories in particular in structures of the brain's reinforcement system (Kelley, 2004). However, the neurophysiological adaptations were not only observed in the reward system, but also in other structures of the brain. A series of studies in animals by Robinson and Kolb (Robinson and Kolb, 1997, 1999, 2004; Robinson et al., 2001; Li et al., 2003; Ferrario et al., 2005) showed that psychoactive drugs, such as cocaine, amphetamine, nicotine, and morphine can cause a number of morphological changes in neocortical neurons, i.e., in areas not considered to be part of the reward system, but rather part of other memory circuits (Eichenbaum, 1997; Milner et al., 1998). These changes, which comprise an increase in neuronal spine density and axonal sprouting, were normally observed during normal, i.e., drug free, learning (Moser et al., 1994). Furthermore, when induced by psychoactive drugs, normal environmental enrichment, was no longer able to induce it (Kolb et al., 2003).

NEUROIMAGING

An activation of cortical memory areas was also shown in various imaging studies in humans during drug exposure or presentation of craving-eliciting cues (Grant et al., 1996; Bonson et al., 2002; Goldstein et al., 2007). Thereby, the brain areas activated during actual drug exposure often overlap with those areas activated during presentation of drug-associated cues (e.g., Breiter et al., 1997; Childress et al., 1999). These findings support the view that psychoactive drugs do not only functionally interact with the brain reward system, but also with other memory systems – if not with the whole brain (Tretter et al., 2009), thus causing acute responses and plastic changes which are similar to those observed during normal learning (Kelley, 2004).

While the review of neurophysiological drug-effects is far from complete, it shows several mechanisms of how an acute drug-induced activation of memory systems may result in fast plasticity which can shape future behavioral responses to drug-cues and the drug itself. How each of them relates specifically to episodic drug memories still has to be shown. It should also be noted, that these effects might reflect merely functional correlates of episodic drug memories during initial/early drug exposure. There are also consummatory episodes remembered during chronic consumption and addiction. However, after repeated drug exposition, many more drug memories are formed, which control future drug directed behaviors (**Figure 1**). Furthermore, episodic memories of a single consummatory episode may consist of rather different components, such as an initial euphoria episode later followed by an aversive withdrawal episode. Both are characterized by quite different neurochemical profiles (I have only discussed the initial effects here), but may result in equally well remembered episodes. Currently this may only suggest that quite different mechanisms may shape episodic drug memories, e.g., in their affective value, which clearly awaits further research.

Another limitation in the interpretation of neurophysiological drug-effects arises from a lack of proper models for episodic drug memories. Virtually all animal models of addiction, such as operant self-administration or conditioned place preference, focus on addiction-related behaviors which all require multiple drug expositions (Olmstead, 2006; Sanchis-Segura and Spanagel, 2006). Coinciding neuronal and functional adaptations in the brain may, thus, reflect more than one type of learning and memory (e.g., Huston et al., 2013). For future research in the episodic memories of drug-effects, a specific animal model would be useful.

CONCLUSION

Here a potential role of episodic drug memories in psychoactive drug use and drug instrumentalization is suggested. Easily accessible verbal reports from human drug users suggest that there are episodic memories with specific drug-related content. These memories are, especially when involving strong emotional responses, one-trial memories with a particularly high extinction resistance. Neurophysiological analyses of drug-effects in the brain provide evidence for strong neurochemical effects of psychoactive drugs in memory processing systems, which outreach those of non-drug stimuli/events. As such, there emerges also a neurophysiological base for episodic drug memories which may influence later consummatory behaviors. A more in depth analysis of the concept suggests that the "What-Where-When" characteristic of episodic memories can be applied equally well to the analysis of episodic drug memories. Altogether, it is suggested to consider episodic drug memories as an important mediator in the establishment of early drug consumption and the transition to drug instrumentalization which should warrant further exploration.

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REFERENCES

Abel, E. L. (1980). *Marihuana: The First Twelve Thousand Years*. New York: Plenum Press.

Aggleton, J. P., and Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav. Brain Sci.* 22, 425–444.

Aggleton, J. P., and Brown, M. W. (2005). Contrasting hippocampal and perirhinal cortex function using immediate early gene imaging. *Q. J. Exp. Psychol. B* 58, 218–233.

Ahmed, S. H. (2010). Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. *Neurosci. Biobehav. Rev.* 35, 172–184.

Amendt, G. (2003). *No Drugs No Future*. Hamburg: Europa Verlag.

Ameri, A. (1999). The effects of cannabinoids on the brain. *Prog. Neurobiol.* 58, 315–348.

American Psychiatric Association. (1994). *Diagnostic Statistical Manual of Mental Disorders*, 4th Edn. (Washington: American Psychiatric Association).

Anderson, S. M., Famous, K. R., Sadri-Vakili, G., Kumaresan, V., Schmidt, H. D., Bass, C. E., et al. (2008). CaMKII: a biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nat. Neurosci.* 11, 344–353.

Argilli, E., Sibley, D. R., Malenka, R. C., England, P. M., and Bonci, A. (2008). Mechanism and time course of cocaine-induced long-term potentiation in the ventral tegmental area. *J. Neurosci.* 28, 9092–9100.

Bardo, M. T. (1998). Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. *Crit. Rev. Neurobiol.* 12, 37–67.

Bardo, M. T., and Bevins, R. A. (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl.)* 153, 31–43.

Bast, T. (2007). Toward an integrative perspective on hippocampal function: from the rapid encoding of experience to adaptive behavior. *Rev. Neurosci.* 18, 253–281.

Belin, D., and Everitt, B. J. (2008). Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* 57, 432–441.

Belin, D., Jonkman, S., Dickinson, A., Robbins, T. W., and Everitt, B. J. (2009). Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. *Behav. Brain Res.* 199, 89–102.

Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., and Everitt, B. J. (2008). High impulsivity predicts the switch to compulsive cocaine-taking. *Science* 320, 1352–1355.

Bilbao, A., Parkitna, J. R., Engblom, D., Perreau-Lenz, S., Sanchis-Segura, C., Schneider, M., et al. (2008). Loss of the Ca2+/calmodulin-dependent protein kinase type IV in dopaminoceptive neurons enhances behavioral effects of cocaine. *Proc. Natl. Acad. Sci. U.S.A.* 105, 17549–17554.

Blokland, A. (1995). Acetylcholine: a neurotransmitter for learning and memory? *Brain Res. Brain Res. Rev.* 21, 285–300.

Boening, J. A. (2001). Neurobiology of an addiction memory. *J. Neural Transm.* 108, 755–765.

Bonson, K. R., Grant, S. J., Contoreggi, C. S., Links, J. M., Metcalfe, J., Weyl, H. L., et al. (2002). Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology* 26, 376–386.

Borgland, S. L., Malenka, R. C., and Bonci, A. (2004). Acute and chronic cocaine-induced potentiation of synaptic strength in the ventral tegmental area: electrophysiological and behavioral correlates in individual rats. *J. Neurosci.* 24, 7482–7490.

Bouton, M. E., and Moody, E. W. (2004). Memory processes in classical conditioning. *Neurosci. Biobehav. Rev.* 28, 663–674.

Bowers, M. S., Chen, B. T., and Bonci, A. (2010). AMPA receptor synaptic plasticity induced by psychostimulants: the past, present, and therapeutic future. *Neuron* 67, 11–24.

Boyd, C. J., McCabe, S. E., Cranford, J. A., and Young, A. (2006). Adolescents' motivations to abuse prescription medications. *Pediatrics* 118, 2472–2480.

Boys, A., and Marsden, J. (2003). Perceived functions predict intensity of use and problems in young polysubstance users. *Addiction* 98, 951–963.

Boys, A., Marsden, J., Griffiths, P., Fountain, J., Stillwell, G., and Strang, J. (1999). Substance use among young people: the relationship between perceived functions and intentions. *Addiction* 94, 1043–1050.

Boys, A., Marsden, J., and Strang, J. (2001). Understanding reasons for drug use amongst young people: a functional perspective. *Health Educ. Res.* 16, 457–469.

Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., et al. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron* 19, 591–611.

Brown, S. A. (1985). Expectancies versus background in the prediction of college drinking patterns. *J. Consult. Clin. Psychol.* 53, 123–130.

Brown, S. A., Goldman, M. S., Inn, A., and Anderson, L. R. (1980). Expectations of reinforcement from alcohol: their domain and relation to drinking patterns. *J. Consult. Clin. Psychol.* 48, 419–426.

Campbell, J. C., Szumlinski, K. K., and Kippin, T. E. (2009). Contribution of early environmental stress to alcoholism vulnerability. *Alcohol* 43, 547–554.

Cauli, O., and Morelli, M. (2005). Caffeine and the dopaminergic system. *Behav. Pharmacol.* 16, 63–77.

Childress, A. R., Mozley, P. D., McElgin, W., Fitzgerald, J., Reivich, M., and O'Brien, C. P. (1999). Limbic activation during cue-induced cocaine craving. *Am. J. Psychiatry* 156, 11–18.

Consolo, S., Caltavuturo, C., Colli, E., Recchia, M., and Di Chiara, G. (1999). Different sensitivity of in vivo acetylcholine transmission to D1 receptor stimulation in shell and core of nucleus accumbens. *Neuroscience* 89, 1209–1217.

de Wit, H., and Stewart, J. (1981). Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology (Berl.)* 75, 134–143.

Dean, L. G., Kendal, R. L., Schapiro, S. J., Thierry, B., and Laland, K. N. (2012). Identification of the social and cognitive processes underlying human cumulative culture. *Science* 335, 1114–1118.

Del Boca, F. K., Darkes, J., Goldman, M. S., and Smith, G. T. (2002). Advancing the expectancy concept via the interplay between theory and research. *Alcohol. Clin. Exp. Res.* 26, 926–935.

Dere, E., Easton, A., Nadel, L., and Huston, J. P. (2008). *Handbook of Episodic Memory*. New York: Elsevier.

Dere, E., Huston, J. P., and De Souza Silva, M. A. (2007). The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. *Neurosci. Biobehav. Rev.* 31, 673–704.

Dere, E., Kart-Teke, E., Huston, J. P., and De Souza Silva, M. A. (2006). The case for episodic memory in animals. *Neurosci. Biobehav. Rev.* 30, 1206–1224.

Deroche-Gamonet, V., Belin, D., and Piazza, P. V. (2004). Evidence for addiction-like behavior in the rat. *Science* 305, 1014–1017.

Di Chiara, G. (1995). The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug Alcohol. Depend.* 38, 95–137.

Di Chiara, G., and Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl. Acad. Sci. U.S.A.* 85, 5274–5278.

Di Chiara, G., and North, R. A. (1992). Neurobiology of opiate abuse. *Trends Pharmacol. Sci.* 13, 185–193.

Dong, L., Bilbao, A., Laucht, M., Henriksson, R., Yakovleva, T., Ridinger, M., et al. (2011). Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking. *Am. J. Psychiatry* 168, 1090–1098.

Dong, Y., Saal, D., Thomas, M., Faust, R., Bonci, A., Robinson, T., et al. (2004). Cocaine-induced potentiation of synaptic strength in dopamine neurons: behavioral correlates in GluRA(-/-) mice. *Proc. Natl. Acad. Sci. U.S.A.* 101, 14282–14287.

Drummond, D. C., Cooper, T., and Glautier, S. P. (1990). Conditioned learning in alcohol dependence: implications for cue exposure treatment. *Br. J. Addict.* 85, 725–743.

Easton, A. C., Lucchesi, W., Lourdusamy, A., Lenz, B., Solati, J., Golub, Y., et al. (2013a). αCaMKII autophosphorylation controls the establishment of alcohol reinforcement by altering dopamine-serotonin balance. *Neuropsychopharmacology* (in press).

Easton, A. C., Lourdusamy, A., Loth, E., Toro, R., Giese, K. P., Kornhuber, J., et al. (2013b). alphaCaMKII gene (CAMK2A) polymorphisms predict spatial working memory performance in humans. *Mol. Psychiatry* (in press).

Eichenbaum, H. (1997). How does the brain organize memories? *Science* 277, 330–332.

Eissenberg, T., and Balster, R. L. (2000). Initial tobacco use episodes in children and adolescents: current knowledge, future directions. *Drug Alcohol. Depend.* 59(Suppl. 1), S41–S60.

EMCDDA. (2012). *European Monitoring Center for Addictive Drugs. State of the Drug Problem 2009.* Available at: http://www.emcdda.europa.eu/publications/annual-report/2012

Everitt, B. J., Hutcheson, D. M., Ersche, K. D., Pelloux, Y., Dalley, J. W., and Robbins, T. W. (2007). The orbital prefrontal cortex and drug addiction in laboratory animals and humans. *Ann. N. Y. Acad. Sci.* 1121, 576–597.

Everitt, B. J., and Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* 8, 1481–1489.

Faleiro, L. J., Jones, S., and Kauer, J. A. (2004). Rapid synaptic plasticity of glutamatergic synapses on dopamine neurons in the ventral tegmental area in response to acute amphetamine injection. *Neuropsychopharmacology* 29, 2115–2125.

Ferrario, C. R., Gorny, G., Crombag, H. S., Li, Y., Kolb, B., and Robinson, T. E. (2005). Neural and behavioral plasticity associated with the transition from controlled to escalated cocaine use. *Biol. Psychiatry* 58, 751–759.

Foltin, R. W., and Haney, M. (2000). Conditioned effects of environmental stimuli paired with smoked cocaine in humans. *Psychopharmacology (Berl.)* 149, 24–33.

Frederiksen, N. J., Bakke, S. L., and Dalum, P. (2012). "No alcohol, no party": an explorative study of young Danish moderate drinkers. *Scand. J. Public Health* 40, 585–590.

Friedman, L. S., Lichtenstein, E., and Biglan, A. (1985). Smoking onset among teens: an empirical analysis of initial situations. *Addict. Behav.* 10, 1–13.

Gawin, F. H. (1991). Cocaine addiction: psychology and neurophysiology. *Science* 251, 1580–1586.

Giese, K. P., Fedorov, N. B., Filipkowski, R. K., and Silva, A. J. (1998). Autophosphorylation at Thr286 of the alpha calcium-calmodulin kinase II in LTP and learning. *Science* 279, 870–873.

Goldberg, S. R. (1975). Stimuli associated with drug injections as events that control behavior. *Pharmacol. Rev.* 27, 325–340.

Goldman, M. S., Brown, S. A., Christiansen, B. A., and Smith, G. T. (1991). Alcoholism and memory: broadening the scope of alcohol-expectancy research. *Psychol. Bull.* 110, 137–146.

Goldstein, R. Z., Tomasi, D., Rajaram, S., Cottone, L. A., Zhang, L., Maloney, T., et al. (2007). Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience* 144, 1153–1159.

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Liu, X., Contoreggi, C., et al. (1996). Activation of memory circuits during cue-elicited cocaine craving. *Proc. Natl. Acad. Sci. U.S.A.* 93, 12040–12045.

Green, A. R., Mechan, A. O., Elliott, J. M., O'Shea, E., and Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol. Rev.* 55, 463–508.

Gustafson, R. (1991). Is the strength and the desirability of alcohol-related expectancies positively related? A test with an adult Swedish sample. *Drug Alcohol. Depend.* 28, 145–150.

Haber, S. N., Fudge, J. L., and McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* 20, 2369–2382.

Hagen, E. H., Sullivan, R. J., Schmidt, R., Morris, G., Kempter, R., and Hammerstein, P. (2009). Ecology and neurobiology of toxin avoidance and the paradox of drug reward. *Neuroscience* 160, 69–84.

Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N. H., Suhaimi, F. W., Vadivelu, R., et al. (2013). From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci. Biobehav. Rev.* 37, 138–151.

Heath, D. B. (2000). *Drinking Occasions: Comparative Perspectives on Alcohol and Culture.* New York: Brunner/Mazel.

Hellemans, K. G., Everitt, B. J., and Lee, J. L. (2006). Disrupting reconsolidation of conditioned withdrawal memories in the basolateral amygdala reduces suppression of heroin seeking in rats. *J. Neurosci.* 26, 12694–12699.

Henn, C., Loffelholz, K., and Klein, J. (1998). Stimulatory and inhibitory effects of ethanol on hippocampal acetylcholine release. *Naunyn Schmiedebergs Arch. Pharmacol.* 357, 640–647.

Heyne, A., May, T., Goll, P., and Wolffgramm, J. (2000). Persisting consequences of drug intake: towards a memory of addiction. *J. Neural Transm.* 107, 613–638.

Huffman, M. A. (2003). Animal self-medication and ethno-medicine: exploration and exploitation of the medicinal properties of plants. *Proc. Nutr. Soc.* 62, 371–381.

Huston, J. P., de Souza Silva, M. A., Topic, B., and Müller, C. P. (2013). What's conditioned in conditioned place preference? *Trends Pharmacol. Sci.* 34, 162–166.

Huston, J. P., Mondadori, C., and Waser, P. G. (1974). Facilitation of learning by reward of post-trial memory processes. *Experientia* 30, 1038–1040.

Huston, J. P., Mueller, C. C., and Mondadori, C. (1977). Memory facilitation by posttrial hypothalamic stimulation and other reinforcers: a central theory of reinforcement. *Neurosci. Biobehav. Rev.* 1, 143–150.

Hyman, S. E., and Malenka, R. C. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat. Rev. Neurosci.* 2, 695–703.

Hyman, S. E., Malenka, R. C., and Nestler, E. J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu. Rev. Neurosci.* 29, 565–598.

Imperato, A., Obinu, M. C., Demontis, M. V., and Gessa, G. L. (1992). Cocaine releases limbic acetylcholine through endogenous dopamine action on D1 receptors. *Eur. J. Pharmacol.* 229, 265–267.

Imperato, A., Obinu, M. C., and Gessa, G. L. (1993a). Effects of cocaine and amphetamine on acetylcholine release in the hippocampus and caudate nucleus. *Eur. J. Pharmacol.* 238, 377–381.

Imperato, A., Obinu, M. C., and Gessa, G. L. (1993b). Stimulation of both dopamine D1 and D2 receptors facilitates in vivo acetylcholine release in the hippocampus. *Brain Res.* 618, 341–345.

Imperato, A., Obinu, M. C., Mascia, M. S., Casu, M. A., Zocchi, A., Cabib, S., et al. (1996). Strain-dependent effects of dopamine agonists on acetylcholine release in the hippocampus: an in vivo study in mice. *Neuroscience* 70, 653–660.

Irvine, E. E., von Hertzen, L. S., Plattner, F., and Giese, K. P. (2006). alphaCaMKII autophosphorylation: a fast track to memory. *Trends Neurosci.* 29, 459–465.

Iversen, L. L. (2000). *The Science of Marihuana.* Oxford: Oxford University Press.

Johanson, C. E., and Fischman, M. W. (1989). The pharmacology of cocaine related to its abuse. *Pharmacol. Rev.* 41, 3–52.

Jones, R. T. (1971). Marihuana-induced "high": influence of expectation, setting and previous drug experience. *Pharmacol. Rev.* 23, 359–369.

Kalivas, P. W., Sorg, B. A., and Hooks, M. S. (1993). The pharmacology and neural circuitry of sensitization to psychostimulants. *Behav. Pharmacol.* 4, 315–334.

Kandel, E. R. (2001). The molecular biology of memory storage: a dialogue between genes and synapses. *Science* 294, 1030–1038.

Kandel, E. R., and Pittenger, C. (1999). The past, the future and the biology of memory storage. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 354, 2027–2052.

Kauer, J. A., and Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nat. Rev. Neurosci.* 8, 844–858.

Kelley, A. E. (2004). Memory and addiction: shared neural circuitry and molecular mechanisms. *Neuron* 44, 161–179.

Kidorf, M., Sherman, M. F., Johnson, J. G., and Bigelow, G. E. (1995). Alcohol expectancies and changes in beer consumption of first-year college students. *Addict. Behav.* 20, 225–231.

Kilts, C. D., Schweitzer, J. B., Quinn, C. K., Gross, R. E., Faber, T. L., Muhammad, F., et al. (2001). Neural activity related to drug craving in cocaine addiction. *Arch. Gen. Psychiatry* 58, 334–341.

Kippin, T. E. (2011). Does drug misinstrumentalization lead to drug abuse? *Behav. Brain Sci.* 34, 316–317.

Knowlton, B. J., Mangels, J. A., and Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science* 273, 1399–1402.

Kolb, B., Gorny, G., Li, Y. L., Samaha, A. N., and Robinson, T. E. (2003). Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens. *Proc. Natl. Acad. Sci. U.S.A.* 100, 10523–10528.

Koob, G. F. (1992). Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci.* 13, 177–184.

Koob, G. F., Sanna, P. P., and Bloom, F. E. (1998). Neuroscience of addiction. *Neuron* 21, 467–476.

Kuntsche, E., Knibbe, R., Gmel, G., and Engels, R. (2005). Why do young people drink? A review of drinking motives. *Clin. Psychol. Rev.* 25, 841–861.

Larsson, A., Edstrom, L., Svensson, L., Soderpalm, B., and Engel, J. A. (2005). Voluntary ethanol intake increases extracellular acetylcholine levels in the ventral tegmental area in the rat. *Alcohol Alcohol.* 40, 349–358.

Lee, J. L., Di Ciano, P., Thomas, K. L., and Everitt, B. J. (2005). Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. *Neuron* 47, 795–801.

Lee, J. L., Milton, A. L., and Everitt, B. J. (2006). Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. *J. Neurosci.* 26, 5881–5887.

Leigh, B. C. (1989). In search of the Seven Dwarves: issues of measurement and meaning in alcohol expectancy research. *Psychol. Bull.* 105, 361–373.

Leigh, B. C., and Stacy, A. W. (2004). Alcohol expectancies and drinking in different age groups. *Addiction* 99, 215–227.

Lende, D. H., and Smith, E. O. (2002). Evolution meets biopsychosociality: an analysis of addictive behavior. *Addiction* 97, 447–458.

Lende, D. H., Leonard, T., Sterk, C. E., and Elifson, K. (2007). Functional methamphetamine use: the insider's perspective. *Addict. Res. Theory* 15, 465–477.

Li, Y. L., Kolb, B., and Robinson, T. E. (2003). The location of persistent amphetamine-induced changes in the density of dendritic spines on medium spiny neurons in the nucleus accumbens and caudate-putamen. *Neuropsychopharmacology* 28, 1082–1085.

Licata, S. C., and Pierce, R. C. (2003). The roles of calcium/calmodulin-dependent and Ras/mitogen-activated protein kinases in the development of psychostimulant-induced behavioral sensitization. *J. Neurochem.* 85, 14–22.

Liu, J., Suncion-Chin, M., Liu, P., and Dopico, A. M. (2006). CaM kinase II phosphorylation of slo Thr107 regulates activity and ethanol responses of BK channels. *Nat. Neurosci.* 9, 41–49.

Lozano, G. A. (1998). Parasitic stress and self-medication in wild animals. *Adv. Stud. Behav.* 27, 291–317.

Mameli, M., Bellone, C., Brown, M. T., and Lüscher, C. (2011). Cocaine inverts rules for synaptic plasticity of glutamate transmission in the ventral tegmental area. *Nat. Neurosci.* 14, 414–416.

Markou, A. (2008). Neurobiology of nicotine dependence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 3159–3168.

McBride, W. J., Le, A. D., and Noronha, A. (2002). Central nervous system mechanisms in alcohol relapse. *Alcohol. Clin. Exp. Res.* 26, 280–286.

McBride, W. J., Murphy, J. M., and Ikemoto, S. (1999). Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. *Behav. Brain Res.* 101, 129–152.

McGaugh, J. L. (2000). Memory – a century of consolidation. *Science* 287, 248–251.

Mello, N. K. (1972). "Behavioral studies of alcoholism," in *Biology of Alcoholism*, eds B. Kissin and H. Begleiter (New York: Plenum Press), 210–219.

Miller, C. S. (2001). Toxicant-induced loss of tolerance. *Addiction* 96, 115–137.

Miller, P. M., Smith, G. T., and Goldman, M. S. (1990). Emergence of alcohol expectancies in childhood: a possible critical period. *J. Stud. Alcohol* 51, 343–349.

Milner, B., Squire, L. R., and Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron* 20, 445–468.

Morris, R. G., Anderson, E., Lynch, G. S., and Baudry, M. (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* 319, 774–776.

Moser, M. B., Trommald, M., and Andersen, P. (1994). An increase in dendritic spine density on hippocampal Ca1 pyramidal cells following spatial-learning in adult-rats suggests the formation of new synapses. *Proc. Natl. Acad. Sci. U.S.A.* 91, 12673–12675.

Müller, C. P., Carey, R. J., Huston, J. P., and De Souza Silva, M. A. (2007a). Serotonin and psychostimulant addiction: focus on 5-HT1A-receptors. *Prog. Neurobiol.* 81, 133–178.

Müller, C. P., De Souza Silva, M. A., and Huston, J. P. (2007b). Double dissociating effects of sensory stimulation and cocaine on serotonin activity in the occipital and temporal cortices. *Neuropharmacology* 52, 854–862.

Müller, C. P., Pum, M. E., Amato, D., Schüttler, J., Huston, J. P., and de Souza Silva, M. A. (2011). The in-vivo neurochemistry of the brain during general anesthesia. *J. Neurochem.* 119, 419–446.

Müller, C. P., De Souza Silva, M. A., DePalma, G., Tomaz, C., Carey, R. J., and Huston, J. P. (2002). The selective serotonin(1A)-receptor antagonist WAY 100635 blocks behavioral stimulating effects of cocaine but not ventral striatal dopamine increase. *Behav. Brain Res.* 134, 337–346.

Müller, C. P., and Huston, J. P. (2007). Dopamine activity in the occipital and temporal cortices of rats: dissociating effects of sensory but not pharmacological stimulation. *Synapse* 61, 254–258.

Müller, C. P., and Schumann, G. (2011a). Drugs as an instrument: a new framework for non-addictive psychoactive drug use. *Behav. Brain Sci.* 34, 293–310.

Müller, C. P., and Schumann, G. (2011b). To use or not to use: expanding the view on non-addictive psychoactive drug consumption and its implications. *Behav. Brain Sci.* 34, 328–347.

Müller, C. P., Thönnessen, H., Barros, M., Tomaz, C., Carey, R. J., and Huston, J. P. (2004). Hippocampus 5-HT(1A)-receptors attenuate cocaine-induced hyperlocomotion and the increase in hippocampal but not nucleus accumbens 5-HT. *Hipppocampus* 14, 710–721.

Müller, C. P., Pum, M. E., Schumann, G., and Huston, J. P. (2010). "The role of serotonin in drug addiction," in *The Behavioral Neurobiology of Serotonin*, eds C. P. Müller and B. L. Jacobs (London: Academic Press), 507–546.

Nesse, R. M., and Berridge, K. C. (1997). Psychoactive drug use in evolutionary perspective. *Science* 278, 63–66.

Nestler, E. J. (2002). Common molecular and cellular substrates of addiction and memory. *Neurobiol. Learn. Mem.* 78, 637–647.

Nestler, E. J. (2008). Review. Transcriptional mechanisms of addiction: role of DeltaFosB. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 3245–3255.

Nestler, E. J., and Aghajanian, G. K. (1997). Molecular and cellular basis of addiction. *Science* 278, 58–63.

O'Brien, C. P., Childress, A. R., Ehrman, R., and Robbins, S. J. (1998). Conditioning factors in drug abuse: can they explain compulsion? *J. Psychopharmacol.* 12, 15–22.

O'Brien, C. P., Testa, T., O'Brien, T. J., Brady, J. P., and Wells, B. (1977). Conditioned narcotic withdrawal in humans. *Science* 195, 1000–1002.

Olmstead, M. C. (2006). Animal models of drug addiction: where do we go from here? *Q. J. Exp. Psychol. (Hove)* 59, 625–653.

O'Malley, P. M., and Johnston, L. D. (2002). Epidemiology of alcohol and other drug use among American college students. *J. Stud. Alc.* 14, 23–39.

Overton, D. A. (1968). Visual cues and shock sensitivity in the control of

T-maze choice by drug conditions. *J. Comp. Physiol. Psychol.* 66, 216–219.
Patrick, M. E., and Maggs, J. L. (2008). Short-term changes in plans to drink and importance of positive and negative alcohol consequences. *J. Adolesc.* 31, 307–321.
Peele, S., and Brodsky, A. (2000). Exploring psychological benefits associated with moderate alcohol use: a necessary corrective to assessments of drinking outcomes? *Drug Alcohol. Depend.* 60, 221–247.
Perry, E., Walker, M., Grace, J., and Perry, R. (1999). Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci.* 22, 273–280.
Piazza, P. V., Deminiere, J. M., Le, M. M., and Simon, H. (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science* 245, 1511–1513.
Pierce, R. C., and Kumaresan, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neurosci. Biobehav. Rev.* 30, 215–238.
Porrino, L. J., Lyons, D., Smith, H. R., Daunais, J. B., and Nader, M. A. (2004). Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *J. Neurosci.* 24, 3554–3562.
Pum, M., Carey, R. J., Huston, J. P., and Müller, C. P. (2007). Dissociating effects of cocaine and d-amphetamine on dopamine and serotonin in the perirhinal, entorhinal, and prefrontal cortex of freely moving rats. *Psychopharmacology (Berl.)* 193, 375–390.
Pum, M. E., Huston, J. P., and Müller, C. P. (2009). The role of cortical serotonin in anxiety and locomotor activity in Wistar rats. *Behav. Neurosci.* 123, 449–454.
Quirion, R., Richard, J., and Wilson, A. (1994). Muscarinic and nicotinic modulation of cortical acetylcholine release monitored by in vivo microdialysis in freely moving adult rats. *Synapse* 17, 92–100.
Rex, A., Marsden, C. A., and Fink, H. (1993). Effect of diazepam on cortical 5-HT release and behaviour in the guinea-pig on exposure to the elevated plus maze. *Psychopharmacology (Berl.)* 110, 490–496.
Richardson, N. R., and Roberts, D. C. S. (1996). Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *J. Neurosci. Methods* 66, 1–11.
Robbins, T. W., Ersche, K. D., and Everitt, B. J. (2008). Drug addiction and the memory systems of the brain. *Ann. N. Y. Acad. Sci.* 1141, 1–21.
Robbins, T. W., and Everitt, B. J. (1999). Drug addiction: bad habits add up. *Nature* 398, 567–570.
Robinson, T. E., Gorny, G., Mitton, E., and Kolb, B. (2001). Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse* 39, 257–266.
Robinson, T. E., and Kolb, B. (1997). Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. *J. Neurosci.* 17, 8491–8497.
Robinson, T. E., and Kolb, B. (1999). Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. *Eur. J. Neurosci.* 11, 1598–1604.
Robinson, T. E., and Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* 47, 33–46.
Rodriguez, E., and Wrangham, R. (1993). Zoopharmacognosy: the use of medicinal plants by animals. *Recent Adv. Phytochem.* 27, 89–105.
Rueter, L. E., Fornal, C. A., and Jacobs, B. L. (1997). A critical review of 5-HT brain microdialysis and behavior. *Rev. Neurosci.* 8, 117–137.
Saal, D., Dong, Y., Bonci, A., and Malenka, R. C. (2003). Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 37, 577–582.
SAMHSA. (2011). *National Survey on Drug Use and Health.* Rockville: Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/NSDUH/2011SummNatFindDetTables/Index.aspx
Sanchis-Segura, C., and Spanagel, R. (2006). Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. *Addict. Biol.* 11, 2–38.
Sarter, M., Hasselmo, M. E., Bruno, J. P., and Givens, B. (2005). Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Res. Brain Res. Rev.* 48, 98–111.
Schultz, W. (2000). Multiple reward signals in the brain. *Nat. Rev. Neurosci.* 1, 199–207.
Schumann, G., Coin, L. J., Lourdusamy, A., Charoen, P., Berger, K. H., Stacey, D., et al. (2011). Genome-wide association and genetic functional studies identify autism susceptibility candidate 2 gene (AUTS2) in the regulation of alcohol consumption. *Proc. Natl. Acad. Sci. U.S.A.* 108, 7119–7124.
Seiden, L. S., Sabol, K. E., and Ricaurte, G. A. (1993). Amphetamine – effects on catecholamine systems and behavior. *Annu. Rev. Pharmacol. Toxicol.* 33, 639–677.
Shaham, Y., Shalev, U., Lu, L., de Wit, H., and Stewart, J. (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl.)* 168, 3–20.
Sher, K. J., Grekin, E. R., and Williams, N. A. (2005). The development of alcohol use disorders. *Annu. Rev. Clin. Psychol.* 1, 493–523.
Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *J. Comp. Physiol. Psychol.* 89, 498–506.
Siegel, S. (1988). Drug anticipation and the treatment of dependence. *NIDA Res. Monogr.* 84, 1–24.
Siegel, S., Hinson, R. E., Krank, M. D., and McCully, J. (1982). Heroin "overdose" death: contribution of drug-associated environmental cues. *Science* 216, 436–437.
Simons, J., Correia, C. J., and Carey, K. B. (2000). A comparison of motives for marihuana and alcohol use among experienced users. *Addict. Behav.* 25, 153–160.
Skogen, J. C., Harvey, S. B., Henderson, M., Stordal, E., and Mykletun, A. (2009). Anxiety and depression among abstainers and low-level alcohol consumers. The Nord-Trondelag Health Study. *Addiction* 104, 1519–1529.
Spanagel, R. (2009). Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol. Rev.* 89, 649–705.
Spealman, R. D., and Goldberg, S. R. (1978). Drug self-administration by laboratory animals: control by schedules of reinforcement. *Annu. Rev. Pharmacol. Toxicol.* 18, 313–339.
Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* 24, 417–463.
Squire, L. R., Knowlton, B., and Musen, G. (1993). The structure and organization of memory. *Annu. Rev. Psychol.* 44, 453–495.
Stacey, D., Bilbao, A., Maroteaux, M., Jia, T., Easton, A. C., Longueville, S., et al. (2012). RASGRF2 regulates alcohol-induced reinforcement by influencing mesolimbic dopamine neuron activity and dopamine release. *Proc. Natl. Acad. Sci. U.S.A.* 109, 21128–21133.
Stacey, D., Clarke, T. K., and Schumann, G. (2009). The genetics of alcoholism. *Curr. Psychiatry Rep.* 11, 364–369.
Stolerman, I. (1992). Drugs of abuse: behavioural principles, methods and terms. *Trends Pharmacol. Sci.* 13, 170–176.
Summers, K. L., and Giacobini, E. (1995). Effects of local and repeated systemic administration of (-)nicotine on extracellular levels of acetylcholine, norepinephrine, dopamine, and serotonin in rat cortex. *Neurochem. Res.* 20, 753–759.
Tani, Y., Saito, K., Imoto, M., and Ohno, T. (1998). Pharmacological characterization of nicotinic receptor-mediated acetylcholine release in rat brain – an in vivo microdialysis study. *Eur. J. Pharmacol.* 351, 181–188.
Tretter, F., Gebicke-Haerter, P. J., Albus, M., an der Heiden, U., and Schwegler, H. (2009). Systems biology and addiction. *Pharmacopsychiatry* 42(Suppl. 1), S11–S31.
Tulving, E. (2001). Episodic memory and common sense: how far apart? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1505–1515.
Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25.
Tupala, E., and Tiihonen, J. (2004). Dopamine and alcoholism: neurobiological basis of ethanol abuse. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 28, 1221–1247.
Tzschentke, T. M. (2007). Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addict. Biol.* 12, 227–462.
Ungless, M. A., Argilli, E., and Bonci, A. (2010). Effects of stress and aversion on dopamine neurons: implications for addiction. *Neurosci. Biobehav. Rev.* 35, 151–156.
Ungless, M. A., Whistler, J. L., Malenka, R. C., and Bonci, A. (2001). Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 411, 583–587.
Vanderschuren, L. J., and Everitt, B. J. (2004). Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 305, 1017–1019.
Vanderschuren, L. J., and Kalivas, P. W. (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical

studies. *Psychopharmacology (Berl.)* 151, 99–120.

Volkow, N. D., Wang, G. J., Ma, Y. M., Fowler, J. S., Wong, C., Jayne, M., et al. (2006). Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drug abusing subjects. *Neuroimage* 32, 1782–1792.

Volkow, N. D., Wang, G. J., Ma, Y. M., Fowler, J. S., Zhu, W., Maynard, L., et al. (2003). Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *J. Neurosci.* 23, 11461–11468.

Waldorf, D., Reinarman, C., and Murphy, S. (1991). *Cocaine Changes: The Experience of Using and Quitting*. Philadelphia: Temple University Press.

Wanat, M. J., and Bonci, A. (2008). Dose-dependent changes in the synaptic strength on dopamine neurons and locomotor activity after cocaine exposure. *Synapse* 62, 790–795.

Wang, M., Vijayraghavan, S., and Goldman-Rakic, P. S. (2004). Selective D2 receptor actions on the functional circuitry of working memory. *Science* 303, 853–856.

Waskow, I. E., Olsson, J. E., Salzman, C., and Katz, M. M. (1970). Psychological effects of tetrahydrocannabinol. *Arch. Gen. Psychiatry* 22, 97–107.

White, N. M. (1989). Reward or reinforcement: what's the difference? *Neurosci. Biobehav. Rev.* 13, 181–186.

White, N. M. (1996). Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* 91, 921–949.

White, N. M., and Milner, P. M. (1992). The psychobiology of reinforcers. *Annu. Rev. Psychol.* 43, 443–471.

Wikler, A., and Pescor, F. T. (1967). Classical conditioning of a morphine abstinence phenomenon, reinforcement of opioid-drinking behavior and "relapse" in morphine-addicted rats. *Psychopharmacologia* 10, 255–284.

Williams, G. V., and Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376, 572–575.

Williams, M. J., and Adinoff, B. (2008). The role of acetylcholine in cocaine addiction. *Neuropsychopharmacology* 33, 1779–1797.

Willuhn, I., Burgeno, L. M., Everitt, B. J., and Phillips, P. E. (2012). Hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine use. *Proc. Natl. Acad. Sci. U.S.A.* 109, 20703–20708.

Wise, R. A. (2002). Brain reward circuitry: insights from unsensed incentives. *Neuron* 36, 229–240.

Wise, R. A. (1994). "A brief history of the anhedonia hypothesis," in *Appetite: Neural and Behavioural Base*, eds C. R. Legg and D. A. Both (Oxford: Oxford University Press), 234–263.

Witten, I. B., Lin, S. C., Brodsky, M., Prakash, R., Diester, I., Anikeeva, P., et al. (2010). Cholinergic interneurons control local circuit activity and cocaine conditioning. *Science* 330, 1677–1681.

Woolf, N. J., and Butcher, L. L. (2011). Cholinergic systems mediate action from movement to higher consciousness. *Behav. Brain Res.* 221, 488–498.

Zinberg, N. E. (1984). *Drug, Set, and Setting: The Basis for Controlled Intoxicant Use*. New Haven: Yale University Press.

Zocchi, A., and Pert, A. (1994). Alterations in striatal acetylcholine overflow by cocaine, morphine, and MK-801: relationship to locomotor output. *Psychopharmacology (Berl.)* 115, 297–304.

Zweifel, L. S., Argilli, E., Bonci, A., and Palmiter, R. D. (2008). Role of NMDA receptors in dopamine neurons for plasticity and addictive behaviors. *Neuron* 59, 486–496.

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Don't be too strict with yourself! Rigid negative self-representation in healthy subjects mimics the neurocognitive profile of depression for autobiographical memory

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Autobiographical memory (AM) comprises representation of both specific (episodic) and generic (semantic) personal information. Depression is characterized by a shift from episodic to semantic AM retrieval. According to theoretical models, this process ("overgeneralization"), would be linked to reduced executive resources. Moreover, "overgeneral" memories, accompanied by a negativity bias in depression, lead to a pervasive negative self-representation. As executive functions and AM specificity are also closely intricate among "non-clinical" populations, "overgeneral" memories could result in depressive emotional responses. Consequently, our hypothesis was that the neurocognitive profile of healthy subjects showing a rigid negative self-image would mimic that of patients. Executive functions and self-image were measured and brain activity was recorded, by means of fMRI, during episodic AMs retrieval in young healthy subjects. The results show an inverse correlation, that is, a more rigid and negative self-image produces lower performances in both executive and specific memories. Moreover, higher negative self-image is associated with decreased activity in the left ventro-lateral prefrontal and in the anterior cingulate cortex, repeatedly shown to exhibit altered functioning in depression. Activity in these regions, on the contrary, positively correlates with executive and memory performances, in line with their role in executive functions and AM retrieval. These findings suggest that rigid negative self-image could represent a marker or a vulnerability trait of depression by being linked to reduced executive function efficiency and episodic AM decline. These results are encouraging for psychotherapeutic approaches aimed at cognitive flexibility in depression and other psychiatric disorders.

Keywords: autobiographical memory, depression, executive functions, self, neuroimaging, anterior cingulate cortex, ventro-lateral prefrontal cortex

INTRODUCTION

Autobiographical memory (AM) is the "long term" memory system involved in the retention and retrieval of personal past events. A distinction between episodic AM (EAM) and semantic AM (SAM) has been proposed by several authors (Conway and Pleydell-Pearce, 2000; Conway, 2001; Tulving, 2002; Piolino et al., 2009; Klein and Gangi, 2010). The former refers to memory for unique events situated in time and space and recollected with phenomenological details and a sense of remembering, whereas the latter concerns decontextualized extended or repeated events and self-knowledge such as the name of one's acquaintances.

Autobiographical memory is impaired in a number of psychiatric disorders including post-traumatic stress disorder (McNally et al., 1994), schizophrenia (Riutort et al., 2003; Harrison and Fowler, 2004; Iqbal et al., 2004), and depression (Brittlebank et al., 1993; Kuyken and Dalgleish, 1995; Brewin et al., 1999; Wessel et al., 2001; Watson et al., 2013). The common pattern of AM impairment in these pathological states is characterized by a specific EAM deficit: patients recalling preferentially "overgeneral" memories (i.e., repeated and extended events) rather than unique episodes with a precise spatio-temporal context.

In depression the "overgenerality" characterizing AM retrieval is accompanied by a particular difficulty in recollecting details, even in the context of specific event retrieval (Lemogne et al., 2006). Interestingly, this lack of specificity has predictive value for the course of depression (Brittlebank et al., 1993; Peeters et al.,

2002; Raes et al., 2006; Hermans et al., 2008). Moreover, there is a large body of evidence showing that "overgeneral" AM is not simply a symptom of depression but can be regarded as a trait marker or vulnerability factor for this disease (Williams et al., 2007). Indeed, even in "non-clinical" populations, reduced memory specificity predicts increased emotional reactivity to stressful events (Mackinger et al., 2000; Gibbs and Rude, 2004; Van Minnen et al., 2005; Bryant et al., 2007; for a review, see Raes et al., 2007).

According to the Self-Memory System model (SMS, Conway and Pleydell-Pearce, 2000; Conway, 2005), specific memories are generally accessed through a hierarchical search starting from general events. This process engages executive functions in order to select relevant information and concurrently inhibit competing information. This theoretical model has been supported by numerous studies reporting that the ability to retrieve specific memories is linked to executive processes such as cognitive flexibility, inhibition, updating, shifting, and working memory (Baddeley and Wilson, 1986; Winthorpe and Rabbitt, 1988; Fivush and Nelson, 2004; Matuszewski et al., 2006; Piolino et al., 2007a,b, 2010; Addis et al., 2008; Raes et al., 2010; Ros et al., 2010; Coste et al., 2011).

Thus, "overgeneral" memories may arise when insufficient executive resources cause the premature break of the memory search at higher hierarchical levels. For instance, reduced AM specificity has been shown to be associated with poor performance in verbal fluency in controls (Williams and Dritschel, 1992) and in participants with eating disorders (Dalgleish et al., 2007). In the same vein, Heeren et al. (2009) have reported a parallel improvement of verbal fluency and AM specificity following a mindfulness training. Verbal fluency is sometimes considered as a measure of cognitive flexibility (Heeren et al., 2009), and more generally as a broad measure of executive control (Rosen and Engle, 1997).

Depressed patients show deficits in several executive functions including inhibition (Linville, 1996; MacQueen et al., 2000; Markela-Lerenc et al., 2006; Gohier et al., 2009) and cognitive flexibility (Naismith et al., 2003; Airaksinen et al., 2004; Meiran et al., 2010). Flexibility difficulties have emerged to be among the most prominent cognitive impairment in depression (Austin et al., 2001). Consequently, executive deficits are a central feature of a number of theoretical models of the depressive pathology (Hasher and Zacks, 1979; Ellis and Ashbrook, 1988; Hertel and Rude, 1991; Barrett et al., 2004). Thus, based on Conway and Pleydell-Pearce's (2000) proposition, the Capture and Rumination, Functional Avoidance, and eXecutive control model (CaRFAX model, Williams et al., 2007) proposes that "overgeneralization" in depression may result from executive impairment, that leads to difficulty in inhibiting inappropriate (i.e., "overgeneral") memories. Recently, however, Watson et al. (2013) did not find any relationship between verbal fluency and memory specificity in depressed patients.

Nevertheless, contrasting results have been reported concerning the role of executive deficit in depression, with some studies reporting a normalization of performance after recovery from recurrent depression (Beblo et al., 1999; Neu et al., 2001), whereas others reported a persistent impairment after remission (Beats et al., 1996; Reischies and Neu, 2000). Biringer et al. (2005) have shown no significant difference between recovered patients and controls on a composite score measuring global executive functioning, although, in the same group, semantic fluency performance was still below that of the controls. Such results could depend on the particular process tested, it has been proposed that executive deficits may be a risk factor for emotional disorders (Nolen-Hoeksema and Watkins, 2011), particularly for depression (Ingram et al., 2008).

Theoretical considerations (James, 1890; Conway and Pleydell-Pearce, 2000; Gardiner, 2001), as well as behavioral ones (Rogers et al., 1977; Symons and Johnson, 1997) along with neuroimaging findings (Fletcher et al., 1996; Konishi et al., 2000; McDermott et al., 2000; Donaldson et al., 2001; Northoff and Bernpohl, 2004; Henson et al., 2005; Buckner et al., 2008; Sajonz et al., 2010; for reviews, see Cavanna and Trimble, 2006; Legrand and Ruby, 2009) suggest that AM and self-referential processing are intrinsically related. The relationship between self-concept and AM has been illustrated by a recent neuroimaging study reporting a correlation between the degree of certainty in self-evaluation and activity in dorso-medial prefrontal cortex (MPFC) (D'Argembeau et al., 2012). The authors proposed that this correlation may reflect the engagement of processes involved in the retrieval, integration, and evaluation of self-related information allowing the construction of a coherent self-image.

Thus, the categorical nature of "overgeneral" memories may contribute to other forms of "overgeneral" thinking found in depressed patients such as global negative self-judgment and "overgeneralization" in self-evaluation. Indeed, recurrent retrieval of "overgeneral" memories leads to categorical self-descriptors ("I am always boring") resulting in a retrieval style closely linked to rumination (Watkins and Teasdale, 2001; Raes et al., 2006; Debeer et al., 2011). Thus, depressed patients' cognition is characterized by negative schemas and a self-focus generating and maintaining a depressed mood and a pessimistic view of the self, the world, and the future (Beck, 1976, 2008; Beck et al., 1979). This negative bias has been associated with executive control impairments (Lo and Allen, 2011; De Lissnyder et al., in press), such as difficulties in inhibiting the processing of negative information (Joormann, 2004; Goeleven et al., 2006; see Gotlib and Joormann, 2010 for review). Such cognitive biases, in particular recurrent negative self-evaluations, are known to be predictive of future depressive symptoms (Carver, 1988; Dent and Teasdale, 1988). Accordingly, Mongrain (1990) demonstrated that high rates of dysfunctional attitudes, characterized by rigid content regarding self-worth leading to poor self-esteem (Mirabel-Sarron et al., 2001), are predictive of subsequent depressive symptoms (Beck, 1967; Beck et al., 1979; Segal and Ingram, 1994).

Cognitive theories posit that information processing and memory retrieval style may constitute a risk factor for the occurrence of depressive episodes. Thus, cognitive dysfunction may be an endophenotype for depression (Hasler et al., 2004). In particular, negative self-schemas (Ingram and Siegle, 2002) and self-evaluations (Carver, 1988; Dent and Teasdale, 1988) as well as rigid attitudes regarding self-judgment (Beck, 1967; Beck et al., 1979; Segal and Ingram, 1994) are known to represent vulnerability factors for depression.

Thus, we hypothesize that a rigid negative self-image in a "non-clinical" population would mimic the neurocognitive profile of

depressed patients. To test our hypothesis, we assessed the subjective self-representation of 20 healthy subjects using a standard evaluation. Moreover, we measured different executive functions with standard neuropsychological tests. Then we asked participants to recall specific AMs while recording their brain activity by means of fMRI.

According to the existing literature (Joiner, 2000; Hammen, 2005; O'Brien et al., 2006; Evraire and Dozois, 2011; Morley and Moran, 2011; for review, see Sowislo and Orth, 2012), we expected to find that subjects showing higher negative self-image should show decreased scores on executive functions and, in turn, in the specificity of AMs. Regarding neuroimaging data, we expected to replicate previous findings on AM retrieval reporting activities in a widespread network encompassing fronto-parietal areas, cortical midline regions, and medial temporal structures (for a recent meta-analysis see Martinelli et al., 2012). Moreover, we predicted a significant correlation between the extent of the crystallized negative self-image and the activity in regions frequently reported as dysfunctional in depression (Brody et al., 1999; Mayberg et al., 1999; Drevets and Price, 2005; Murrough et al., 2011), in particular in lateral prefrontal cortex and anterior cingulate cortex (ACC) which are also linked to executive functions and memory retrieval (Ochsner et al., 2004; Kringelbach and Rolls, 2004; Ochsner and Gross, 2005; Niendam et al., 2012).

MATERIALS AND METHODS

PARTICIPANTS

Twenty healthy young volunteers (25–44 years old, mean = 29.2 ± 5.55, 10 women) all right-handed (according to the Edinburgh Handedness Inventory; Oldfield, 1971) and native French speakers participated to the study. All participants gave their informed written consent as required by the local ethic committee (CPP Ile de France 3 n°2687). Exclusion criteria included presence of history of alcohol or substance abuse, head trauma, major diseases affecting brain functions, neuropsychiatric disorders such as clinical depression (tested with the Mini-International Neuropsychiatric Interview, Sheehan et al., 1998). Moreover, all participants were under the cutoff score on the French version of the Beck Depression Inventory (BDI-21, Beck et al., 1988; Bouvard and Cottraux, 1996, cutoff score >14; mean = 2.65 ± 2.53).

SELF-CONCEPT ASSESSMENT

Each subject fulfilled the Tennessee Self-Concept Scale (TSCS, Fitts and Warren, 1996: French version Duval et al., 2007). This scale assesses the multidimensionality of the self over six domains (family, personal, social, moral, physical, academic), and contains 82 descriptive statements (e.g., "I am an honest person") that have to be rated on a five-point scale (always false, mostly false, partly false/partly true, mostly true, always true) according to how well they match the participant's personality. Two standard scores were computed: (1) the degree of certainty (TSCS-C) (for a comparable method, see Addis and Tippett, 2004; Naylor and Clare, 2008) was measured through the amount of responses rated "1" (always false) or "5" (always true) and reflects "the degree of certainty about the way one sees oneself, thus reflecting the extent to which a definite sense of identity is expressed" (Naylor and Clare, 2008, p. 595). A more definite sense of self has been shown to reflect a less nuanced and a more crystallized and rigid self-concept (Klein and Gangi, 2010; Martinelli et al., 2013; Picard et al., in press); (2) the total score of the TSCS (TSCS-V) that reflects the global valence of the self (i.e., direction of the self, Addis and Tippett, 2004) and adds up the separate TSCS scores of identity, satisfaction, and behavior. High scores indicate a positive self-concept and higher self-esteem. Finally, a "negative crystallization score" (NCS) was computed by dividing the degree of certainty by the total score (each score being previously transformed into *z* score), so the higher the NCS score the more the self-concept was crystallized and negative.

NEUROPSYCHOLOGICAL MEASURES

In order to characterize executive and working memory functions, we administered to the participants the following standard tests: the running span (Morris and Jones, 1990; Quinette et al., 2003; total score), the Stroop test (Stroop, 1935; interference score), and trail making test (Reitan, 1958, TMT B-A) to assess updating, inhibition, and shifting functions respectively (Miyake et al., 2000); verbal fluencies (Cardebat et al., 1990, sum of animal and letter P fluency), and digit and visuo-spatial spans (sum of backward and forward spans, Wechsler, 2000) to assess cognitive control and working memory functions. All scores were scaled in the same direction, so that higher scores reflect better performance.

NEUROIMAGING PROCEDURE

Pre-scanning interview

In the pre-scanning interview, exclusion and inclusion criteria were verified by means of a clinical examination and psychometric tests. Then the TSCS and neuropsychological tests were administered to participants. In addition, subjects completed the Taste and Interest Questionnaire (TIQ) that was employed to create personal cues to trigger AM retrieval in the scanning session. The aim of this questionnaire was to collect information in order to create personalized cues for each participant without directly asking for descriptions of past memories to avoid re-encoding memories (Viard et al., 2010; Addis et al., 2011). Participants were informed that the purpose of the questionnaire was to obtain a description of their personality based on information about their main life interests. They had no prior knowledge of the aim of the fMRI task, preventing the possibility for participants of searching for memories linked to their taste and interests between the two sessions. The questionnaire concerned their personal lives from their birth to 5 years ago. It consists of a list of 220 interests including leisure, food, drink, transport, places where they lived, holidays, jobs, studies. For each item, the participants had to answer whether it was personally pertinent or not, rated by 1 and 0 respectively. When an item was pertinent, they had to rate how important (from 0 to 10) and frequent (Frequent/Rare) the activity or interest had been in their life. An activity or interest was used as a cue for episodic AM retrieval if it was pertinent, important (>5), and rare. Twenty-four cues were created for each subject. Examples of activity assessed in the TIQ and the procedure to create cues is illustrated in the **Table A1** in Appendix.

Episodic autobiographical memory task

The participants were first invited to take part in a training session before the fMRI scanning. Participants received detailed

explanations on the nature of the task and participated in a brief simulation of the experiment on a laptop. They were instructed to recall EAMs elicited by the cues and to press a button when a memory was recalled. EAMs were defined as memories of a single event that occurred at a specific time and place, of short duration, lasting less than 24 h. Participants were instructed to mentally relive personal episodes prompted by cues and to recollect affective and perceptual details (such as time, location, perceptions, feelings, scenery, and people present in the scene) (e.g.: "a unique memory linked to a trip in Italy"). After instructions, participants were trained on three trials with the experimenter providing feedback concerning the pertinence of the responses. The cues used for training were different from those used during the scanning session.

Scanning session

During fMRI recording, cues were visually presented in white font on a black background projected on a screen viewed by means of a mirror incorporated into the head-coil. E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) in combination with an Integrated Functional Imaging System (IFIS) was used for the presentation and timing of stimuli and collection of responses. Responses were made on an MR-compatible two-buttons box. Participants completed four functional scans in a single session. Each functional scan was composed of six items. Each trial lasted 26 s with the following time-course: the cue was presented for 5 s, followed by a white cross at the center of the screen for 19 s, then the cross turned red for 3 s informing the participants of the end of the present trial and the arrival of the next one. Participants were instructed to press a button as soon as they accessed a memory.

Post scan interview

Participants were asked to recall again each EAM retrieved in the scanner in order to check that memories met minimal criteria of specificity (single events, situated in time and place, lasting less than 24 h, e.g., "the day of the visit of the exhibition 'The man on the moon' in the Palace of Tokyo museum in Paris, in August 2009"). The subsequent analyses were performed only on memories that met all the above mentioned criteria.

Episodic AMs were rated for specificity on standard scales (Levine et al., 2002; Piolino et al., 2009). More precisely, the presence of specific spatial and temporal details, and other contextual and phenomenological details in each evocation was noted (one point by type of detail, max. 4; e.g., "I remember my visit in the Palace of Tokyo as if I was still there, being together with Chiara in a room of the exhibition in the first floor in the dark to see the TV reports and talking with other visitors. . ., it was 6:00 p.m., after then we settled down in the restaurant of the outdoor museum in front of the Seine. . ."). We computed for each participant a global ratio of specificity (EPI score) totaling up the sum of spatio-temporal, other contextual and phenomenological details, divided by the number of EAM.

fMRI METHOD

MRI data acquisition

All data were acquired with a 3 T scanner (MR 750, General Electric Healthcare, Little Chalfont, UK). The anatomical scan used an inversion recovery 3-D T1-weighted gradient-echo sequence images (TE = 4.3 ms, TR = 11.2 ms, TI = 400 ms, matrix = 384 × 384, slice thickness = 1.2 mm). Functional images were acquired using a gradient-echo echoplanar (EPI) sequence (TE = 30 ms, TR = 2000 ms, flip angle = 90°, matrix = 64 × 64, slice thickness = 3 mm, 42 contiguous sections). The first four volumes of each functional run were discarded in order to allow longitudinal magnetization to approach equilibrium.

Pre-processing of fMRI data

All data were processed using SPM5 software (Statistical Parametric Mapping 5, Welcome Dept. Cognitive Neurology, UK; www.fil.ion.ucl.ac.uk/spm). Standard pre-processing procedures were applied to MRI data. EPI volumes were corrected for slice timing, realigned to the first image, co-registered with the high-resolution T_1-weighted image and normalized into the Montreal Neurological Institute (MNI) template. Finally, the normalized EPI volumes were smoothed using an isotropic Gaussian kernel filter of 5 mm full-width half-maximum.

First level analysis of fMRI data

Only correct trials were used for the subsequent analyses. A trial was considered as correct if (1) the participant had pressed the button during the trial (indicating retrieval) and (2) the description of the memory during the debriefing corresponded to EAM (see above). Memory retrieval (i.e., access or strategic research phase) was modeled by convolving the time period between cue presentation and subjects' response with the hemodynamic response function (HRF). For each subject, General Linear Model was used to estimate the parameters of interest. Parameters of movement were also included in the model as regressors of no interest. A whole brain t-test was computed to estimate the contrast of interest for each subject: EAM vs. rest. Then, contrasts for each individual were used for second-level analyses.

Second-level analysis of fMRI data

We computed a whole brain t-test using first level contrasts for each subject. An activation map resulting from this analysis was then used to mask subsequent correlation analysis. The rationale of this choice was that we were only interested in correlations in areas showing a significant activation. Threshold for the whole brain t-test was fixed at $p < 0.01$ corrected for multiple comparison using the false discovery rate (FDR) with an extended threshold of $k = 20$.

Correlations

We computed correlations between signal change in regions showing a significant activity at the group level and the NCS using the multiple regression model in SPM in which we entered contrast images as well as the NCS for each subject as a covariate. The threshold for this analysis was fixed at $p < 0.01$ (uncorrected) with an extended threshold of $k = 10$. Then we extracted percentage signal change of clusters showing a significant correlation using Marsbar toolbox (Brett et al., 2002) and calculated correlations between signal change and the executive and EAM scores outside SPM using STATISTICA7©.

RESULTS

BEHAVIORAL RESULTS

Participants showed a high percentage of correct trials (CR, mean 87.85 ± 7.70) and a rapid response time (RT, mean 2.28 ± 0.94 s). NCS correlated negatively with inhibition, verbal fluency, and working memory performances. A trend for a negative correlation between NCS and the episodic score was found ($r = -0.44$, $p = 0.054$). Interestingly, the two basic scores of the TSCS, certainty (TSCS-C) and valence (TSCS-V) of self-concept, did not singularly correlate with executive functions and the episodic score. The episodic score correlated positively with performance on executive functions, namely inhibition, shifting (TMT B-A), verbal fluency, and working memory. For detailed results see **Table 1**.

fMRI RESULTS

Activation during EAM retrieval

We reported activations in several clusters encompassing lateral (mainly on the left side) and medial frontal regions and posterior medial regions. In particular we found activations in cortical midline structures comprising MPFC, ACC, posterior cingulate (PCC), and precuneus. Moreover insula, cerebellum, inferior parietal, and occipital regions as well as lateral and medial temporal regions comprising the hippocampus were found (**Figure 1**). The list of local activation maxima is reported on **Table 2**.

Correlation between brain activations, neuropsychological, and EAM scores

We observed negative correlations between the NCS and the dorsal ACC (dACC) and the ventro-lateral prefrontal cortex (vLPFC) in the left side (**Figure 2**). See **Table 3** for peaks coordinates. A positive correlation was reported between verbal fluency and both regions, whereas only the dACC showed a significant correlation with inhibition performance. Moreover, for correlations between activity in these regions and the other scores of interest we found a positive correlation with episodic scores. The basic scores of the TSCS did not show significant correlations with the other variables. For detailed results see **Table 4**.

A series of partial correlations (Bravais–Pearson) were calculated between the NCS, the episodic score, and activity in the dACC and vLPFC, separately controlling for inhibition, fluency,

Table 1 | Correlations between self-concept, episodic and neuropsychological scores.

	NCS	TSCS-C	TSCS-V	EPI	FLU	INHIB	TMT B-A	R-SPAN	WM	CR	RT
NCS		0.040	−0.365	−0.438	**−0.626**	**−0.582**	−0.271	−0.203	**−0.449**	0.149	0.011
p		0.869	0.114	0.054	**0.003**	**0.007**	0.248	0.391	**0.047**	0.532	0.965
TSCS-C	0.040		**0.748**	−0.118	−0.227	−0.051	0.120	0.114	−0.058	0.086	−0.321
p	0.869		**0.000**	0.622	0.337	0.832	0.613	0.632	0.809	0.719	0.168
TSCS-V	−0.365	**0.748**		0.040	0.207	0.194	0.202	0.369	0.346	−0.020	−0.094
p	0.114	**0.000**		0.867	0.381	0.412	0.394	0.110	0.135	0.934	0.692
EPI	−0.438	−0.118	0.040		**0.523**	**0.545**	**0.451**	0.411	**0.668**	0.363	0.076
p	0.054	0.622	0.867		**0.018**	**0.013**	**0.046**	0.072	**0.001**	0.115	0.750
FLU	**−0.626**	−0.227	0.207	**0.523**		**0.478**	**0.536**	**0.492**	**0.596**	0.264	−0.008
p	**0.003**	0.337	0.381	**0.018**		**0.033**	**0.015**	**0.027**	**0.006**	0.260	0.975
INHIB	**−0.582**	−0.051	0.194	**0.545**	**0.478**		−0.275	**0.498**	**0.581**	−0.074	0.088
p	**0.007**	0.832	0.412	**0.013**	**0.033**		0.241	**0.025**	**0.007**	0.755	0.712
TMT B-A	−0.271	0.120	0.202	**0.451**	**0.536**	−0.275		0.429	0.417	**0.460**	−0.209
p	0.248	0.613	0.394	**0.046**	**0.015**	0.241		0.059	0.068	**0.041**	0.377
R-SPAN	−0.203	0.114	0.369	0.411	**0.492**	**0.498**	0.429		**0.689**	0.100	0.174
p	0.391	0.632	0.110	0.072	**0.027**	**0.025**	0.059		**0.001**	0.677	0.462
WM	**−0.449**	−0.058	0.346	**0.668**	**0.596**	**0.581**	0.417	**0.689**		0.134	0.435
p	**0.047**	0.809	0.135	**0.001**	**0.006**	**0.007**	0.068	**0.001**		0.573	0.055
CR	0.149	0.086	−0.020	0.363	0.264	−0.074	**0.460**	0.100	0.134		−0.189
p	0.532	0.719	0.934	0.115	0.260	0.755	**0.041**	0.677	0.573		0.425
RT	0.011	−0.321	−0.094	0.076	−0.008	0.088	−0.209	0.174	0.435	−0.189	
p	0.965	0.168	0.692	0.750	0.975	0.712	0.377	0.462	0.055	0.425	

NCS, negative crystallization score; TSCS-C, TSCS, certainty score; TSCS-V, TSCS, valence score; EPI, episodic score of EAM; FLU, verbal fluency score; INHIB, interference score Stroop, inhibition; TMTB-A, trail making test B-A score, shifting; R-SPAN, running span, updating; WM, working memory score, digit and visuo-spatial spans; CR, correct responses; RT, response time. Correlations written in bold font are significant ($p < 0.05$ to $p < 0.001$).

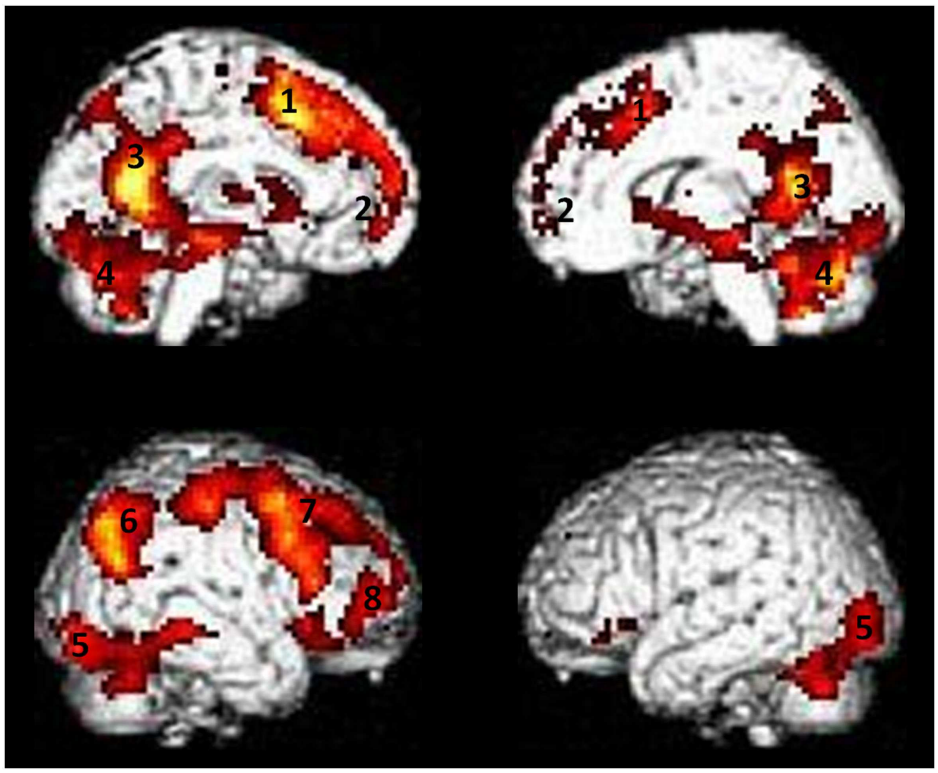


FIGURE 1 | Areas showing activity during retrieval of episodic autobiographical memory. (1) Dorsal anterior cingulate cortex (dACC), (2) medial prefrontal cortex (MPFC), (3) posterior cingulate cortex/precuneus (PCC/precuneus), (4) cerebellum, (5) occipital cortex, (6) posterior parietal cortex (PPC), (7) dorso-lateral prefrontal cortex (dLPFC), (8) ventro-lateral prefrontal cortex (vLPFC). Results are superimposed to a single subject rendering and are significant at a threshold of $p < 0.01$ corrected for multiple comparison using the false discovery rate (FDR) with an extended threshold of $k = 20$.

and working memory scores. When controlling for inhibition, fluency, or working memory performance the correlation between NCS and the episodic score disappeared. Moreover, when controlling for the fluency score, the correlations between the NCS and the vLPFC, and between the episodic score and the same region become marginally significant. See **Table 5** for detailed results.

DISCUSSION

In the present study we assessed, through standard tests, self-concept, executive functions' profile as well as brain activations during an EAM retrieval task in a group of young healthy subjects. In line with our hypotheses we reported that participants with a rigid negative self-representation tend to retrieve less detailed memories and show poorer performance on executive scores, in particular on inhibition, verbal fluency, and working memory. Interestingly, the valence and the certainty of self-representation taken alone did not seem to be linked either with executive functions, or with EAM performance. This result suggests that a negative self-representation accompanied by a flexible cognitive style would not necessarily lead to "depressive-like" cognitive functioning, and that a rigid self schema would not be inadaptative if not centered on negative content (see Martinelli et al., 2012). Moreover, two regions that were activated in the access or strategic research phase of EAM retrieval, the dACC and the left vLPFC, showed a negative correlation with the NCS, a positive correlation with verbal fluency, and a positive correlation with the episodic scores. Finally, only activity in dACC correlated significantly with inhibition.

Our results are coherent with models of AM retrieval assigning a central role to executive functions in the hierarchical search of episodic details (Baddeley and Wilson, 1986; Conway and Fthenaki, 2000; Conway and Pleydell-Pearce, 2000). Moreover, the negative correlation between executive and the NCS scores is in agreement with previous proposals of executive dysfunction as a trait marker or risk factor for depression (Hasler et al., 2004). Overall, our results suggest that executive functions could have a central role in both inefficient search mechanisms during EAM retrieval and in the construction of a rigid or schematic self-representation, concerning, above all, negative content. Of particular interest is the fact that the marginally significant correlation we found between the NCS and episodic details was removed when controlling for executive functions. Thus, executive functions may mediate the relationship between the NCS and low episodic score. This is in line with the CaRFAX model that assigns a central role to executive deficits in reduced AM specificity in depression (Williams et al., 2007). Also, our neuroimaging results indicated that activity

Table 2 | List of regions activated during memory retrieval.

Lobe	Labels	BA	*t*	MNI		
				x	*y*	*z*
Frontal	ACC	32	13.91	−6	15	45
	Mid. front.	6	11.81	−39	9	54
	Prec. gyr.	4	8.36	−36	−27	54
	SMA	6	8.04	−6	18	63
	Mid. front.	8	7.81	−24	27	51
	vLPFC	44	7.71	−51	12	36
	dLPFC	9	7.59	−18	36	45
	vLPFC	45	6.53	−54	24	15
	dLPFC	9	6.37	−9	54	36
	vMPFC	11	6.34	−9	60	−6
	Mid. front.	10	6.26	−33	48	12
	Mid. CC	23	6.09	0	−36	33
	Prec. gyr.	6	5.98	−33	−18	63
	vLPFC	47	5.59	−36	45	3
	vLPFC	47	4.61	30	27	0
Parietal	PCC	23	12.28	−6	−57	18
	Pre. cun.	7	11.53	6	−57	−48
	Inf. par.	7	10.37	−36	−72	42
	Ang. gyr.	39	9.98	−48	−69	30
	Inf. par.	40	8.72	−39	−33	48
	Sup. par.	7	7.54	−30	−69	51
	Postc. gyr.	3	7.31	−45	−27	51
Temporal	Fus. gyr.	37	10.3	−27	−36	−18
	Fus. gyr.	37	8.43	30	−57	−27
	Inf. temp.	20	6.56	−54	−39	−12
	Hipp.		5.54	−21	−18	−15
	pHipp.		4.94	24	−18	−21
Occipital	Calcarine	17	13.48	−9	−60	12
	Lingual gyr.	17	12.18	12	−54	9
	Calcarine	18	8.55	9	−72	−30
	Inf. occ.	19	8.01	−39	−87	−6
	Inf. occ.	18	6.29	−30	−90	−6
	Inf. occ.	19	6.21	39	−75	−18
Other	Cerebellum		6.65	0	−66	−30
	Insula		5.95	−30	24	−3

BA, Brodmann area; ACC, anterior cingulate cortex; Mid. front., middle frontal gyrus; Prec. gyr., precentral gyrus; SMA, supplementary motor area; vLPFC, ventro-lateral prefrontal cortex; dLPFC, dorso-lateral prefrontal cortex; vMPFC, ventro-medial prefrontal cortex; Mid. CC, middle cingulate cortex; PCC, posterior cingulate cortex; Pre. cun., precuneus; Inf. par., inferior parietal gyrus; Ang. gyr., angular gyrus; Sup. par., superior parietal gyrus; Postc. gyr., postcentral gyrus; Fus. gyr., fusiform gyrus; Inf. temp., inferior temporal gyrus; Hipp., hippocampus; pHipp, parahippocampus; Lingual gyr., lingual gyrus; Inf. occ., inferior occipital gyrus.

in dACC and vLPFC that were engaged in EAM retrieval, negatively correlated with the NCS and, in turn, positively correlated with executive functions and episodic details, suggesting shared neurocognitive processes.

The ACC has been divided into a dorsal "cognitive" and a rostral "emotional" component (Bush et al., 1998; Whalen et al., 1998; Etkin et al., 2006). The dACC is commonly reported to be recruited during tasks eliciting cognitive control, conflict resolution, and error monitoring (Bush et al., 2000; Beckmann et al., 2009). It has been found to be activated, together with other fronto-parietal regions, across diverse executive functions such as flexibility, inhibition, shifting, and working memory (Hedden and Gabrieli, 2010; Niendam et al., 2012). Regarding inhibition specifically, the positive correlation we found between dACC activity and the interference score corroborates previous findings reporting specific activity in the dACC during Stroop tasks (Bush et al., 1998). Moreover, ACC activity elicited during a Stroop task has been shown to be lower after a negative mood induction (Nixon et al., 2012).

Thus, dACC can be seen as supporting superordinate cognitive control processes (Niendam et al., 2012). This is in line with its role in EAM retrieval and with the pattern of correlations reported in the present study. Indeed, as mentioned above, during memory search, executive functions are supposed to be recruited to select relevant information and concurrently inhibit competing information.

Moreover, in healthy subjects, the dACC is known to exert an inhibitory influence over the limbic system that is devoted to emotional processing (Bush et al., 2000; Shafritz et al., 2006). In individuals with depression, hypo-activation in dACC is assumed to disrupt this inhibitory control leading to the attentional bias for negative information (Greicius et al., 2007). Indeed, in a task requiring participants to disengage attention from negative irrelevant material, depressed patients showed increased activity of the dACC, suggesting a greater cognitive and neural resources requirement during controlled emotional processing (Foland-Ross et al., 2013). Thus, the lower activity of dACC in subjects with greater NCS scores and the concurrent positive correlation between its activity and the inhibition score seems to mimic the neural profile associated with impaired emotional control in depression. This assumption appears quite relevant considering that the Stroop task has been shown to activate the dACC in healthy controls but not in subjects with mood-disorders (George et al., 1997).

Convincing evidence suggests that lateral prefrontal cortex is involved in high-order control processes regulating cognition and behavior (Miller, 2000; Miller et al., 2002; Petrides, 2005). Within prefrontal cortex, a dorso-ventral functional specialization has been proposed. The dorso-lateral prefrontal cortex would be engaged in on-line monitoring and manipulation of information in working memory, whereas the vLPFC would underpin active selection, comparison, and judgment of information held in short and long term memory (Petrides, 1995, 2002, 2005). Concerning memory retrieval, the same author reported that vLPFC, corresponding to BA 45 and 47, would be essential when active strategic retrieval of memories is at stake, but not during automatic retrieval. More recently, Badre and Wagner (2007) proposed a further subdivision of the vLPFC into the anterior vLPFC, corresponding to BA 47, and the mid-vLPFC, composed by BA 45. They reported evidence for a two-process account of controlled memory retrieval mechanisms implemented in the vLPFC with the anterior portion engaged in strategic processes and top down facilitation

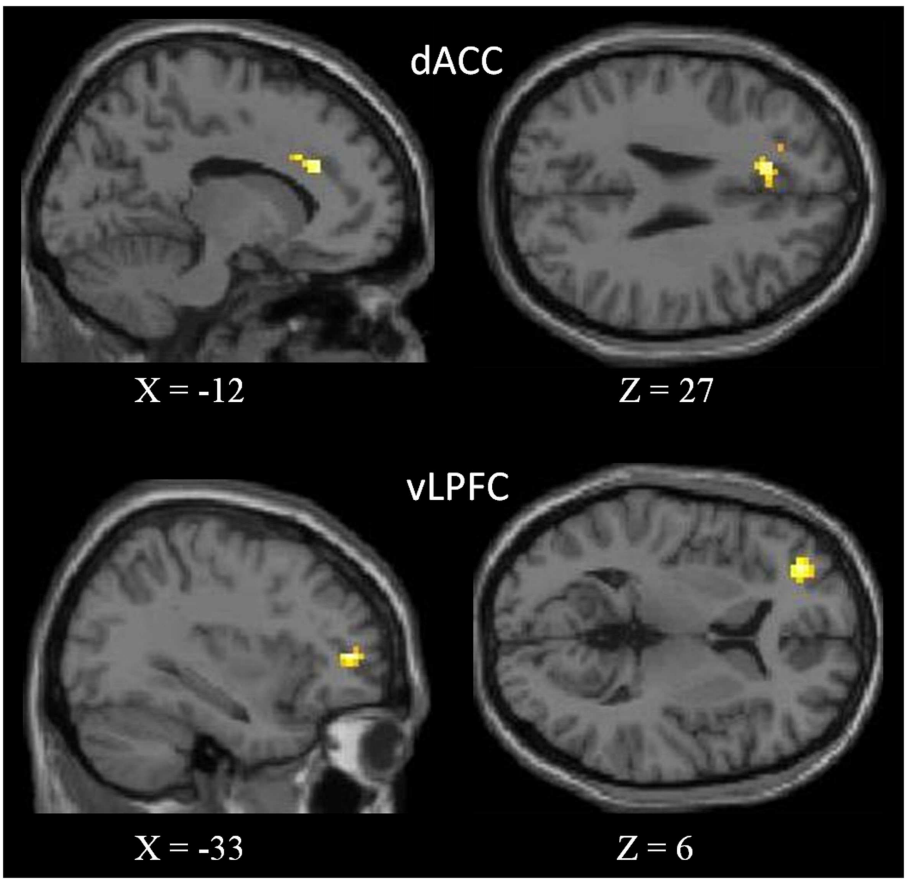


FIGURE 2 | Areas showing negative correlation with the NCS. In the upper part of figure, the dorsal anterior cingulate cortex (dACC), and in the bottom, the ventro-lateral prefrontal cortex (vLPFC). Results are superimposed to a single subject T1-weighted image normalized to the MNI stereotaxic space. Results are significant at a threshold of $p < 0.01$ (uncorrected) with an extended threshold of $k = 10$.

of relevant information and the mid-vLPFC that would be especially in charge of post retrieval selection of relevant information between competing representations. This account of the anterior vLPFC involvement in effortful strategic memory retrieval fits well with its activation in our task and the correlation found with performance on verbal fluency tasks.

Besides its strategic role in memory retrieval, vLPFC is also known to modulate emotional responses of the amygdala through an attentional biasing mechanism (Wager et al., 2008). Moreover, vLPFC is frequently altered in depression at both the functional (Brody et al., 1999; Mayberg et al., 1999) and structural levels (mainly BA 47, Drevets and Price, 2005). These changes may participate in explaining the depression-related negative bias. Indeed, there is evidence of attenuated neural response in the vLPFC of depressed patients when responding to targets that were preceded by sad distracters (Wang et al., 2008; Dichter et al., 2009). Moreover, rumination on bad feelings and past experiences is maintained in depressed patients by an impaired cognitive control mechanism associated with the hypoactivation of the left prefrontal regions, in particular of the vLPFC (Ochsner et al., 2004; Ray et al., 2005; Gotlib and Hamilton, 2008).

Table 3 | List of regions showing a correlation with the CNS.

Lobe	Labels	BA	*t*	MNI		
				x	*y*	*z*
Frontal	vLPFC	47	4.24	−33	45	6
	dACC	32	3.76	−12	27	27

BA, Brodmann area; dACC, dorsal anterior cingulate cortex; vLPFC, ventro-lateral prefrontal cortex.

Based on the aforementioned literature on abnormalities in emotional processing in depression, Murrough et al. (2011) proposed a model suggesting that depression-related functional changes are characterized by an imbalance between the cognitive control, implemented in the PFC, and the emotional system, based on limbic structures. In other words, the under-activity of the former regions is thought to mediate executive impairment and to contribute to explaining the failure of cognitive control on emotion in depression.

Interestingly, Beevers et al. (2010) reported that patients with a mild to moderate depression experienced difficulty recruiting

Table 4 | Correlations between brain activity self-concept, episodic and neuropsychological scores.

	NCS	TSCS-C	TSCS-V	EPI	FLU	INHIB	TMT B-A	R-SPAN	WM
dACC	**−0.717**	−0.001	0.153	**0.630**	**0.504**	**0.587**	0.285	0.114	0.330
p	**0.000**	0.996	0.520	**0.003**	**0.024**	**0.007**	0.224	0.634	0.155
vLPFC	**−0.632**	0.156	0.233	**0.591**	**0.538**	0.311	0.332	0.127	0.333
p	**0.003**	0.511	0.324	**0.006**	**0.015**	0.182	0.152	0.593	0.151

NCS, negative crystallization score; TSCS-C, TSCS, certainty score; TSCS-V, TSCS, valence score; EPI, episodic score of EAM; FLU, verbal fluency score; INHIB, interference score Stroop, inhibition; TMTB-A, trail making test B-A score, shifting; R-SPAN, running span, updating; WM, working memory score, digit and visuo-spatial spans; dACC, dorsal anterior cingulate cortex; vLPFC, ventro-lateral prefrontal cortex. Correlations written in bold font are significant ($p < 0.05$ to $p < 0.001$).

Table 5 | Partial correlations between brain activity, self-concept, and episodic score, controlling for executive functions performances.

	NCS	EPI	dACC	vLPFC
INHIB				
NCS		−0.18	**−0.57**	**−0.58**
p		0.469	**0.011**	**0.009**
EPI	−0.18		**0.46**	**0.53**
p	0.469		**0.049**	**0.020**
dACC	**−0.57**	**0.46**		**0.77**
p	**0.011**	**0.049**		**0.000**
vLPFC	**−0.58**	**0.53**	**0.77**	
p	**0.009**	**0.020**	**0.000**	
FLU				
NCS		−0.17	**−0.60**	−0.45
p		0.499	**0.007**	0.053
EPI	−0.17		**0.50**	0.43
p	0.499		**0.030**	0.066
dACC	**−0.60**	**0.50**		**0.70**
p	**0.007**	**0.030**		**0.001**
vLPFC	−0.45	0.43	**0.70**	
p	0.053	0.066	**0.001**	
WM				
NCS		−0.21	**−0.67**	**−0.57**
p		0.395	**0.002**	**0.010**
EPI	−0.21		**0.58**	**0.52**
p	0.395		**0.009**	**0.021**
dACC	**−0.67**	**0.58**		**0.75**
p	**0.002**	**0.009**		**0.000**
vLPFC	**−0.57**	**0.52**	**0.75**	
p	**0.010**	**0.021**	**0.000**	

NCS, negative crystallization score; EPI, episodic score of EAM; INHIB, interference score Stroop, inhibition; FLU, verbal fluency score; WM, working memory score; dACC, dorsal anterior cingulate cortex; vLPFC, ventro-lateral prefrontal cortex. Correlations written in bold font are significant ($p < 0.05$ to $p < 0.001$).

regions involved in cognitive control, notably vLPFC, when processing emotional information, whereas activity of cerebral regions that typically subserve emotional experience *per se*, such as amygdala and orbital PFC, were not associated with depressive symptoms. The authors concluded that more severe forms of depression may be necessary before neural activity in these emotional processing regions would be attained (Siegle et al., 2007; Hamilton and Gotlib, 2008).

In summary, according to the aforementioned literature, we propose that the neurocognitive profile of people with a negative crystallized self-representation would mimic that of mildly to moderately depressed patients. In particular, the negative rigid self-representation might result from diminished executive functions resources that, in turn, could affect EAM. This cognitive-profile pattern would be expressed at the neural level as an inefficient recruitment of prefrontal regions normally involved in cognitive control.

Our findings could have a potential impact on research on neurocognitive markers of depression and are encouraging for a psychotherapeutic approach promoting cognitive flexibility, such as novel cognitive behavioral therapies integrating mindfulness practices. Indeed, mindfulness meditation has been shown to produce structural and functional changes in the lateral PFC and in the ACC (Chiesa and Serretti, 2010; Tang et al., 2012), and to improve autobiographical specificity in formerly depressed patients (Williams et al., 2000) and in healthy subjects (Heeren et al., 2009). Moreover, in the latter study improved AM was correlated with enhanced executive functions.

In conclusion, we showed in healthy young participants, that the degree of crystallized negative self-representation mimics the cognitive profile reported in depression concerning executive functions and AM, and that this pattern could be mediated by an inefficient recruitment of prefrontal structures involved in cognitive control of emotional response.

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REFERENCES

Addis, D. R., Roberts, R. P., and Schacter, D. L. (2011). Age-related neural changes in autobiographical remembering and imagining. *Neuropsychologia* 49, 3656–3669.

Addis, D. R., and Tippett, L. J. (2004). Memory of myself: autobiographical memory and identity in Alzheimer's disease. *Memory* 12, 56–74.

Addis, D. R., Wong, A. T., and Schacter, D. L. (2008). Age-related changes in the episodic simulation of future events. *Psychol. Sci.* 19, 33–41.

Airaksinen, E., Larsson, M., Lundberg, I., and Forsell, Y. (2004). Cognitive functions in depressive disorders: evidence from a population-based study. *Psychol. Med.* 34, 83–91.

Austin, M. P., Mitchell, P., and Goodwin, G. M. (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *Br. J. Psychiatry* 178, 200–206.

Baddeley, A. D., and Wilson, B. (1986). "Amnesia, autobiographical memory and confabulation," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 225–252.

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–2901.

Barrett, L. F., Tugade, M. M., and Engle, R. W. (2004). Individual differences in working memory capacity and dual process theories of the mind. *Psychol. Bull.* 130, 553–573.

Beats, B., Sahakian, B., and Levy, R. (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol. Med.* 26, 591–603.

Beblo, T., Baumann, B., Bogerts, B., Wallesch, C. W., and Herrmann, M. (1999). Neuropsychological correlates of major depression: a short term follow-up. *Cogn. Neuropsychiatry* 4, 333–341.

Beck, A. T. (1967). *Depression: Clinical, Experimental, and Theoretical Aspects.* New York: Hoeber.

Beck, A. T. (1976). *Cognitive Therapy and the Emotional Disorders.* New York: Penguin Books.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am. J. Psychiatry* 165, 969–977.

Beck, A. T., Rush, A. J., Shaw, B. F., and Emery, G. (1979). *Cognitive Therapy of Depression.* New York: Guilford.

Beck, A. T., Steer, R. A., and Garbin, M. G. J. (1988). Psychometric properties of the Beck Depression Inventory twenty-five years of evaluation. *Clin. Psychol. Rev.* 8, 77–100.

Beckmann, M., Johansen-Berg, H., and Rushworth, M. F. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J. Neurosci.* 29, 1175–1190.

Beevers, C. G., Clasen, P., Stice, E., and Schnyer, D. (2010). Depression symptoms and cognitive control of emotion cues: a functional magnetic resonance imaging study. *Neuroscience* 167, 97–103.

Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., et al. (2005). Executive function improvement upon remission of recurrent unipolar depression. *Eur. Arch. Psychiatry Clin. Neurosci.* 255, 373–380.

Bouvard, M., and Cottraux, J. (1996). *Protocoles et échelles d'évaluation en psychiatrie et en psychologie.* Paris: Masson.

Brett, M., Anton, J. L., Valbregue, R., and Poline, J. B. (2002). *8th International Conference on Functional Mapping of the Human Brain, June 2-6*, Sendai. Available at: CD-ROM in NeuroImage. 16. Region of interest analysis using an SPM toolbox [abstract].

Brewin, C. R., Reynolds, M., and Tata, P. (1999). Autobiographical memory processes and the course of depression. *J. Abnorm. Psychol.* 108, 511–517.

Brittlebank, A. D., Scott, J., Williams, J. M. G., and Ferrier, I. N. (1993). Autobiographical memory in depression: state or trait marker? *Br. J. Psychiatry* 162, 118–121.

Brody, A. L., Saxena, S., Silverman, D. H., Alborzian, S., Fairbanks, L. A., Phelps, M. E., et al. (1999). Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psych. Res.* 91, 127–139.

Bryant, R. A., Sutherland, K., and Guthrie, R. M. (2007). Impaired specific autobiographical memory as a risk factor for posttraumatic stress after trauma. *J. Abnorm. Psychol.* 116, 837–841.

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38.

Bush, G., Luu, P., and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci. (Regul. Ed.)* 4, 215–222.

Bush, G., Whalen, P. J., Rosen, B. R., Jenike, M. A., McInerney, S. C., and Rauch, S. L. (1998). The counting Stroop: an interference task specialized for functional neuroimaging – validation study with functional MRI. *Hum. Brain Mapp.* 6, 270–282.

Cardebat, D., Doyon, B., Puel, M., Goulet, P., and Joanette, Y. (1990). Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. *Acta Neurol. Belg.* 90, 207–217.

Carver, C. S. (1988). Generalization, adverse events, and development of depressive symptoms. *J. Pers.* 66, 607–619.

Cavanna, A. E., and Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583.

Chiesa, A., and Serretti, A. A. (2010). Systematic review of neurobiological and clinical features of mindfulness meditations. *Psychol. Med.* 40, 1239–1252.

Conway, M. A. (2001). Sensory-perceptual episodic memory and its context: autobiographical memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1375–1384.

Conway, M. A. (2005). Memory and the self. *J. Mem. Lang.* 53, 594–628.

Conway, M. A., and Fthenaki, A. (2000). "Disruption and loss of autobiographical memory," in *Handbook of Neuropsychology*, 2nd Edn, Vol. 2, eds F. Boller and J. Grafman (Amsterdam: Elsevier), 281–312.

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–288.

Coste, C., Agar, N., Petit Four, A. L., Quinette, P., Guillery, B., Azouvi, P., et al. (2011). Relationship between executive fonctions and short-term feature binding in retrograde autobiographical memory in severe traumatic brain injury. *Cortex* 47, 771–786.

Dalgleish, T., Williams, J. M. G., Golden, A. M. J., Perkins, N., Barrett, L. F., Barnard, P. J., et al. (2007). Reduced specificity of autobiographical memory and depression: the role of executive processes. *J. Exp. Psychol. Gen.* 136, 23–42.

D'Argembeau, A., Jedidi, H., Balteau, E., Bahri, M., Phillips, C., and Salmon, E. (2012). Valuing one's self: medial prefrontal involvement in epistemic and emotive investments in self-views. *Cereb. Cortex* 22, 659–667.

De Lissnyder, E., Koster, E. H. W., and De Raedt, R. (in press). Emotional interference in working memory is related to rumination. *Cogn. Ther. Res.*

Debeer, E., Raes, F., Mark, J., Williams, G., and Hermans, D. (2011). Context-dependent activation of reduced autobiographical memory specificity as an avoidant coping style. *Emotion* 11, 1500–1506.

Dent, J., and Teasdale, J. D. (1988). Negative cognition and the persistence of depression. *J. Abnorm. Psychol.* 97, 29–34.

Dichter, G. S., Felder, J. N., and Smoski, M. J. (2009). Affective context interferes with cognitive control in unipolar depression: an fMRI investigation. *J. Affect. Disord.* 14, 131–142.

Donaldson, D. I., Petersen, S. E., Ollinger, J. M., and Buckner, R. L. (2001). Dissociating state and item components of recognition memory using fMRI. *Neuroimage* 13, 129–142.

Drevets, W. C., and Price, J. L. (2005). "Neuroimaging and neuropathological studies of mood disorders," in *Biology of Depression: From Novel Insights to Therapeutic Strategies*, ed. J. W. M. Licinio (Weinheim: Wiley-VCH Verlag GmbH & Co.,).

Duval, C., Eustache, F., and Piolino, P. (2007). Multidimensional self, autobiographical memory and aging. *Psychol. Neuropsychiatr. Vieil.* 5, 179–192.

Ellis, H. C., and Ashbrook, P. W. (1988). "Resource allocation model of the effects of depressed mood states on memory," in *Affect, Cognition, and Social Behaviour*, ed. J. Forgas (Toronto, ON: Hogrefe), 25–43.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51, 871–882.

Evraire, L. E., and Dozois, D. J. A. (2011). An integrative model of excessive reassurance seeking and negative feedback seeking in the development and maintenance of depression. *Clin. Psychol. Rev.* 31, 1291–1303.

Fitts, W., and Warren, W. (1996). *Tennessee Self-Concept Scale Manual (Second Edition).* Los Angeles: Western Psychological Services.

Fivush, R., and Nelson, K. (2004). Culture and language in the emergence of autobiographical memory. *Psychol. Sci.* 15, 573–577.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S., and Dolan,

R. J. (1996). Brain activity during memory retrieval. The influence of imagery and semantic cueing. *Brain* 119, 1587–1596.

Foland-Ross, L. C., Hamilton, J. P., Joormann, J., Berman, M. G., Jonides, J., and Gotlib, I. H. (2013). The neural basis of difficulties disengaging from negative irrelevant material in major depression. *Psychol. Sci.* 24, 334–344.

Gardiner, J. M. (2001). Episodic memory and autonoetic consciousness: a first-person approach. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1351–1361.

George, M. S. E. C., Ketter, T. A., Parekh, P. I., Rosinsky, N., Ring, H., Pazzeglia, P. J., et al. (1997). Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). *J. Neuropsychiatry Clin. Neurosci.* 9, 55–63.

Gibbs, B. R., and Rude, S. S. (2004). Overgeneral autobiographical memory as depression vulnerability. *Cogn. Ther. Res.* 28, 511–526.

Goeleven, E., De Raedt, R., Baert, S., and Koster, E. H. W. (2006). Deficient inhibition of emotional information in depression. *J. Affect. Disord.* 93, 149–157.

Gohier, B., Ferracci, L., Surguladze, S. A., Lawrence, E., El-Hage, W., Kefi, M. Z., et al. (2009). Cognitive inhibition and working memory in unipolar depression. *J. Affect. Disord.* 116, 100–105.

Gotlib, I. H., and Hamilton, J. P. (2008). Neuroimaging and depression: current status and unresolved issues. *Curr. Dir. Psychol. Sci.* 17, 159–163.

Gotlib, I. H., and Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu. Rev. Clin. Psychol.* 6, 285–312.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., et al. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol. Psychiatry* 62, 429–437.

Hamilton, J. P., and Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biol. Psychiatry* 63, 1155–1162.

Hammen, C. (2005). Stress and depression. *Annu. Rev. Clin. Psychol.* 1, 293–319.

Harrison, C. L., and Fowler, D. (2004). Negative symptoms, trauma, and autobiographical memory: an investigation of individuals recovering from psychosis. *J. Nerv. Ment. Dis.* 192, 745–753.

Hasher, L., and Zacks, R. T. (1979). Automatic and effortful processes in memory. *J. Exp. Psychol. Gen.* 108, 356–388.

Hasler, G., Drevets, W. C., Manji, H. K., and Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29, 1765–1781.

Hedden, T., and Gabrieli, J. D. (2010). Shared and selective neural correlates of inhibition, facilitation, and shifting processes during executive control. *Neuroimage* 51, 421–431.

Heeren, A., Van Broeck, N., and Philippot, P. (2009). The effects of mindfulness on executive processes and autobiographical memory specificity. *Behav. Res. Ther.* 47, 403–409.

Henson, R. N., Hornberger, M., and Rugg, M. D. (2005). Further dissociating the processes involved in recognition memory: an FMRI study. *J. Cogn. Neurosci.* 17, 1058–1073.

Hermans, D., Vandromme, H., Debeer, E., Raes, F., Demyttenaere, K., Brunfaut, E., et al. (2008). Overgeneral autobiographical memory predicts diagnostic status in depression. *Behav. Res. Ther.* 46, 668–677.

Hertel, P. T., and Rude, S. (1991). Depressive deficits in memory: focusing attention improves subsequent recall. *J. Exp. Psychol. Gen.* 120, 301–309.

Ingram, R. E., and Siegle, G. J. (2002). "Methodological issues in depression research: not your father's oldsmobile," in *Handbook of Depression*, 3rd Edn, eds I. Gotlib and C. Hammen (New York: Guilford Press).

Ingram, R. E., Steidtmann, D. K., and Bistricky, S. L. (2008). "Information processing: attention and memory," in *Risk Factors in Depression*, eds K. S. Dobson and D. J. A. Dozois (San Diego, CA: Academic Press), 145–169.

Iqbal, Z., Birchwood, M., Hemsley, D., Jackson, C., and Morris, E. (2004). Autobiographical memory and post-psychotic depression in first episode psychosis. *Br. J. Clin. Psychol.* 43, 97–104.

James, W. (1890). *Principles of Psychology*. Chicago: University of Chicago Press.

Joiner, T. E., Jr. (2000). Depression's vicious scree: self-propagating and erosive processes in depression chronicity. *Clin. Psychol. Sci. Pr.* 7, 203–218.

Joormann, J. (2004). Attentional bias in dysphoria: the role of inhibitory processes. *Cogn. Emot.* 18, 125–147.

Klein, S. B., and Gangi, C. E. (2010). The multiplicity of self: neuropsychological evidence and its implications for the self as a construct in psychological research. *Ann. N. Y. Acad. Sci.* 1191, 1–15.

Konishi, S., Wheeler, M. E., Donaldson, D. I., and Buckner, R. L. (2000). Neural correlates of episodic retrieval success. *Neuroimage* 12, 276–286.

Kringelbach, M. L., and Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog. Neurobiol.* 72, 341–372.

Kuyken, W., and Dalgleish, T. (1995). Autobiographical memory and depression. *Br. J. Clin. Psychol.* 33, 89–92.

Legrand, D., and Ruby, P. (2009). What is self-specific? Theoretical investigation and critical review of neuroimaging results. *Psychol. Rev.* 116, 252–282.

Lemogne, C., Piolino, P., Friszer, S., Claret, A., Girault, N., Jouvent, R., et al. (2006). Episodic autobiographical memory in depression: specificity, autonoetic consciousness and self-perspective. *Conscious. Cogn.* 15, 258–268.

Levine, B., Cabeza, R., McIntosh, A. R., Black, S. E., Grady, C. L., and Stuss, D. T. (2002). Functional reorganisation of memory after traumatic brain injury: a study with H(2)(15)0 positron emission tomography. *J. Neurol. Neurosurg. Psychiatr.* 73, 173–181.

Linville, P. (1996). "Attention inhibition: does it underlie ruminative thought?," in *Ruminative Thoughts. Advances in Social Cognition*, Vol. 9, ed. R. S. Wyer Jr. (Mahwah, NJ: Lawrence Erlbaum), 121–133.

Lo, B. C. Y., and Allen, N. B. (2011). Affective bias in internal attention shifting among depressed youth. *Psychiatry Res.* 187, 125–129.

Mackinger, H. F., Loschin, G. G., and Leibetseder, M. M. (2000). Prediction of postnatal affective changes by autobiographical memories. *Eur. Psychol.* 5, 52–61.

MacQueen, G. M., Tipper, S. P., Young, L. T., Joffe, R. T., and Levitt, A. J. (2000). Impaired distractor inhibition on a selective attention task in unmedicated, depressed subjects. *Psychol. Med.* 30, 557–564.

Markela-Lerenc, J., Kaiser, S., Fiedler, P., Weisbrod, M., and Mundt, C. (2006). Stroop performance in depressive patients: a preliminary report. *J. Affect. Disord.* 94, 261–267.

Martinelli, P., Anssens, A., Sperduti, M., and Piolino, P. (2013). The influence of normal aging and Alzheimer's disease in autobiographical memory highly related to the self. *Neuropsychology* 27, 69–78.

Martinelli, P., Sperduti, M., and Piolino, P. (2012). Neural substrates of the self-memory system: new insights from a meta-analysis. *Hum. Brain Mapp.* doi:10.1002/hbm.22008

Matuszewski, V., Piolino, P., de la Sayette, V., Lalevée, C., Pèlerin, A., Dupuy, B., et al. (2006). Retrieval mechanisms for autobiographical memories: insights from the frontal variant of frontotemporal dementia. *Neuropsychologia* 44, 2386–2397.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., et al. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatr.* 156, 675–682.

McDermott, K. B., Jones, T. C., Petersen, S. E., Lageman, S. K., and Roediger, H. L. (2000). Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: an event-related fMRI study. *J. Cogn. Neurosci.* 12, 965–976.

McNally, R. J., Litz, B. T., Prassas, A., Shin, L. N., and Weathers, F. (1994). Emotional priming and autobiographical memory in posttraumatic stress disorder. *Cogn. Emot.* 8, 351–368.

Meiran, N., Diamond, G. M., Todor, D., and Nemtes, B. (2010). Cognitive rigidity in unipolar depression and obsessive compulsive disorder: examination of task switching, Stroop, working memory updating and post-conflict adaptation. *Psychiatry Res.* 185, 149–156.

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nat. Rev. Neurosci.* 1, 59–65.

Miller, E. K., Freedman, D. J., and Wallis, J. D. (2002). The prefrontal cortex: categories, concepts and cognition. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1123–1136.

Mirabel-Sarron, C., Vera, L., and Samuel-Lajeunesse, B. (2001). Estime de soi et dépression. *Ann. Méd-Psychol.* 159, 144–148.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., and Howerter, A. (2000). The unity and diversity of executive functions and their contribution to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100.

Mongrain, M. (1990). "Motivational aspects of vulnerable personality styles," in *Presentation at the Graduate Student Colloquium of the D.O. Hebb lecture series* (Montreal: McGill).

Morley, T. E., and Moran, G. (2011). The origins of cognitive vulnerability in early childhood: mechanisms linking early attachment to later depression. *Clin. Psychol. Rev.* 31, 1071–1082.

Morris, N., and Jones, D. M. (1990). Habituation to irrelevant speech: effects on a visual short-term memory task. *Percept. Psychophys.* 47, 291–297.

Murrough, J. W., Iacoviello, B., Neumeister, A., Charney, D. S., and Iosifescu, D. V. (2011). Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. *Neurobiol. Learn. Mem.* 96, 553–563.

Naismith, S. L., Hickie, I. B., Turner, K., Little, C. L., Winter, V., Ward, P. B., et al. (2003). Neuropsychological performance in patients with depression is associated with clinical, etiological and genetic risk factors. *J. Clin. Exp. Neuropsychol.* 25, 866–877.

Naylor, E., and Clare, L. (2008). Awareness of memory functioning, autobiographical memory and identity in early-stage dementia. *Neuropsychol. Rehabil.* 18, 590–606.

Neu, P., Kiesslinger, U., Schlattmann, P., and Reischies, F. (2001). Time-related cognitive deficiency in four different types of depression. *Psychiatry Res.* 103, 237–247.

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., and Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci.* 12, 241–268.

Nixon, E., Liddle, P. F., Nixon, N. L., and Liotti, M. (2012). On the interaction between sad mood and cognitive control: the effect of induced sadness on electrophysiological modulations underlying Stroop conflict processing. *Int. J. Psychophysiol.* doi:10.1016/j.ijpsycho.2012.11.014

Nolen-Hoeksema, S., and Watkins, E. R. (2011). A heuristic for developing transdiagnostic models of psychopathology: explaining multifinality and divergent trajectories. *Perspect. Psychol. Sci.* 6, 589–609.

Northoff, G., and Bermpohl, F. (2004). Cortical midline structures and the self. *Trends Cogn. Sci.* 8, 102–107.

O'Brien, E. J., Bartoletti, M., and Leitzel, J. D. (2006). "Self-esteem, psychopathology, and psychotherapy," in *Self-esteem Issues and Answers: A Sourcebook of Current Perspectives*, ed. M. H. Kernis (New York: Psychology Press), 306–315.

Ochsner, K. N., and Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn. Sci.* 9, 242–249.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., et al. (2004). For better or for worse: neural systems supporting the cognitive downand up-regulation of negative emotion. *NeuroImage* 23, 483–499.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.

Peeters, F., Wessel, L., Merckelbach, H., and Boon-Vermeeren, M. (2002). Autobiographical memory specificity and the course of major depressive disorder. *Compr. Psychiatry* 43, 344–350.

Petrides, M. (1995). Functional organization of the human frontal cortex for mnemonic processing. Evidence from neuroimaging studies. *Ann. N. Y. Acad. Sci.* 769, 85–96.

Petrides, M. (2002). The mid-ventrolateral prefrontal cortex and active mnemonic retrieval. *Neurobiol. Learn. Mem.* 78, 528–538.

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 360, 781–795.

Picard, L., Mayor-Dubois, C., Meader, F., Kalenzaga, S., Duval, C., Abram, M., et al. (in press). Functional independence within the self-memory system: new insights from two cases of developmental amnesia. *Cortex.*

Piolino, P., Chételat, G., Matuszewski, V., Landeau, B., De La Sayette, V., Eustache, F., et al. (2007a). In search of autobiographical memories: a PET study in frontotemporal dementia. *Neuropsychologia* 45, 2730–2743.

Piolino, P., Desgranges, B., Manning, L., North, P., Jokic, F., and Eustache, F. (2007b). Autobiographical memory, the sense of recollection and executive functions after severe closed head injury. *Cortex* 2, 176–195.

Piolino, P., Coste, C., Martinelli, P., Macé, A. M., Quinette, P., Guillery-Gerard, B., et al. (2010). Reduced specificity of autobiographical memory and aging: do the executive and feature binding functions of working memory have a role? *Neuropsychologia* 48, 429–440.

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329.

Quinette, P., Guillery, B., Desgranges, B., de la Sayette, V., Viader, F., and Eustache, F. (2003). Working memory and executive functions in transient global amnesia. *Brain* 126, 1917–1934.

Raes, F., Hermans, D., Williams, J. M. G., and Eelen, P. (2006). Reduced autobiographical memory specificity and affect regulation. *Cogn. Emot.* 20, 402–429.

Raes, F., Hermans, D., Williams, J. M. G., and Eelen, P. (2007). A sentence completion procedure as an alternative to the autobiographical memory test for assessing overgeneral memory in non-clinical populations. *Memory* 15, 495–507.

Raes, F., Verstraeten, K., Bijttebier, P., Vasey, M. W., and Dalgleish, T. (2010). Inhibitory control mediates the relationship between depressed mood and overgeneral memory recall in children. *J. Clin. Child Adolesc. Psychol.* 39, 276–281.

Ray, R. D., Ochsner, K. N., Cooper, J. C., Robertson, E. R., Gabrieli, J. D. E., and Gross, J. J. (2005). Individual differences in trait rumination and the neural systems supporting cognitive reappraisal. *Cogn. Affect. Behav. Neurosci.* 5, 156–168.

Reischies, F., and Neu, P. (2000). Comorbidity of mild cognitive disorder and depression – a neuropsychological analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* 4, 186–193.

Reitan, R. (1958). Validity of the Trail Making Test as an indication of organic brain damage. *Percept. Mot. Skills* 8, 271–276.

Riutort, M., Cuervo, C., Danion, J. M., Peretti, C. S., and Salame, P. (2003). Reduced levels of specific autobiographical memories in schizophrenia. *Psychiatry Res.* 117, 35–45.

Rogers, T. B., Kuiper, N. A., and Kirker, W. S. (1977). Self-reference and the encoding of personal information. *J. Pers. Soc. Psychol.* 35, 677–688.

Ros, L., Latorre, J. M., and Serrano, J. P. (2010). Working memory capacity and overgeneral autobiographical memory in young and older adults. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 17, 89–107.

Rosen, V. M., and Engle, R. W. (1997). The role of working memory capacity in retrieval. *J. Exp. Psychol. Gen.* 126, 211–227.

Sajonz, B., Kahnt, T., Margulies, D. S., Park, S. Q., Wittmann, A., and Stoy, M. (2010). Delineating self-referential processing from episodic memory retrieval: common and dissociable networks. *Neuroimage* 50, 1606–1617.

Segal, Z. V., and Ingram, R. E. (1994). Priming and construct activation in test of cognitive vulnerability to unipolar depression. *Clin. Psychol. Rev.* 14, 663–695.

Shafritz, K. M., Collins, S. H., and Blumberg, H. P. (2006). The interaction of emotional and cognitive neural systems in emotionally guided response inhibition. *Neuroimage* 31, 468–475.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 59, 22–33.

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., and Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol. Psychiatry* 61, 198–209.

Sowislo, J. F., and Orth, U. (2012). Does low self-esteem predict depression and anxiety? a meta-analysis of longitudinal studies. *Psychol. Bull.* 139, 213–240.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662.

Symons, C. S., and Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol. Bull.* 121, 371–394.

Tang, Y. Y., Lu, Q., Fan, M., Yang, Y., and Posner, M. I. (2012). Mechanisms of white matter changes induced by meditation. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10570–10574.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25.

Van Minnen, A., Wessel, I., Verhaak, C., and Smeenk, J. (2005). The relationship between autobiographical memory specificity and depressed mood following a stressful life event: a prospective study. *Br. J. Clin. Psychol.* 44, 405–415.

Viard, A., Lebreton, K., Chételat, G., Desgranges, B., Landeau, B., Young, A., et al. (2010). Patterns of hippocampal – neocortical interactions in the retrieval of episodic autobiographical memories across the entire

life-span of aged adults. *Hippocampus* 20, 153–165.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., and Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59, 1037–1050.

Wang, L., LaBar, K. S., Smoski, M., Rosenthal, M. Z., Dolcos, F., Lynch, T. R., et al. (2008). Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. *Psychiatry Res.* 163, 143–155.

Watkins, E., and Teasdale, J. D. (2001). Rumination and overgeneral memory in depression: effects of self-focus and analytic thinking. *J. Abnorm. Psychol.* 110, 353–357.

Watson, L. A., Bertsen, D., Kuyken, W., and Watkins, E. R. (2013). Involuntary and voluntary autobiographical memory specificity as a function of depression. *J. Behav. Ther. Exp. Psychiatry* 44, 7–13.

Wechsler, D. (2000). *Wechsler Adults Intelligence Scale, 3rd Edn*, Paris: Les Editions du Centre de Psychologie Appliquée.

Wessel, I., Meeren, M., Peeters, F., Arntz, A., and Merckelbach, H. (2001). Correlates of autobiographical memory specificity: the role of depression, anxiety and childhood trauma. *Behav. Res. Ther.* 39, 409–421.

Whalen, P. J., Bush, G., McNally, R. J.,Wilhelm, S., McInerney, S. C., Jenike, M. A., et al. (1998). The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol. Psychiatry* 44, 1219–1228.

Williams, J. M., Teasdale, J. D., Segal, Z. V., and Soulsby, J. (2000). Mindfulness-based cognitive therapy reduces overgeneral autobiographical memory in formerly depressed patients. *J. Abnorm. Psychol.* 109, 150–155.

Williams, J. M. G., Barnhofer, T., Crane, C., Hermans, D., Raes, F., Watkins, E., et al. (2007). Autobiographical memory specificity and emotional disorder. *Psychol. Bull.* 113, 122–148.

Williams, J. M. G., and Dritschel, B. (1992). "Categoric and extended autobiographical memories," in *Theoretical Perspectives on Autobiographical Memory*, eds M. A. Conway, D. C. Rubin, H. Spinnler, and W. A. Wagenaar (Dordrecht: Kluwer Academic), 391–410.

Winthorpe, C., and Rabbitt, P. A. (1988). "Working memory capacity, IQ, age, and the ability to recount autobiographical events," in *Practical Aspects of Memory: Current Research and Issues II*, eds M. M. Gruneberg, P. E. Morris, and R. N. Sykes (Chichester: Wiley), 175–179.

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APPENDIX

Table A1 | Excerpt of the Taste and Interest Questionnaire (TIQ).

Activities	Pertinence	Importance	Frequency
TRAVELS			
France	1	7	F
Abroad	1	8	F
Asia	**1**	**9**	**R**
North America	0		
South America	0		
Africa	**1**	**9**	**R**
North Europe	1	6	F
South Europe	1	8	F
East Europe	0		
PHYSICAL ACTIVITIES			
Sports (general)	1	8	F
Team sports	0		
Water sports	0		
Tennis	1	4	R
Golf	**1**	**8**	**R**
Athletics	0		
Relaxation	**1**	**9**	**R**
Equitation	1	10	F
Dance	0		

Activities were selected as a cue for autobiographical recall only if they were pertinent, important (>5), and rare. Items marked in bold are examples of activities selected according the above mentioned criteria.

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Episodic memories in anxiety disorders: clinical implications

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The aim of this review is to summarize research on the emerging role of episodic memories in the context of anxiety disorders (AD). The available literature on explicit, autobiographical, and episodic memory function in AD including neuroimaging studies is critically discussed. We describe the methodological diversity of episodic memory research in AD and discuss the need for novel tests to measure episodic memory in a clinical setting. We argue that alterations in episodic memory functions might contribute to the etiology of AD. We further explain why future research on the interplay between episodic memory function and emotional disorders as well as its neuroanatomical foundations offers the promise to increase the effectiveness of modern psychological treatments. We conclude that one major task is to develop methods and training programs that might help patients suffering from AD to better understand, interpret, and possibly actively use their episodic memories in a way that would support therapeutic interventions and counteract the occurrence of symptoms.

Keywords: episodic memory, autobiographical memory, cognitive behavioral therapy, anxiety disorders, explicit memory, post-traumatic stress disorder, panic disorder, obsessive–compulsive disorder

INTRODUCTION

DIAGNOSTIC CRITERIA OF ANXIETY DISORDERS

The diagnostic criteria for the classification of anxiety disorders (AD) have been steadily refined during the last few decades. AD are debilitating mental disorders that include specific phobia, generalized anxiety disorder (GAD), social phobia, and panic disorder (PD) (according to DSM-5 criteria) as well as post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD) (according to the ICD-10 criteria, which include PTSD and OCD in the group of AD). Some common symptoms of AD are excessive rumination, worrying, fear about the future, and active and passive avoidance behavior of the real or imagined fearful stimuli, situations, or events. It is very likely that operant and classical fear conditioning contribute strongly to the development, persistence, and generalization of inappropriate anxiety responses and that AD can be most parsimoniously explained by the principles of learning theory (Bouton et al., 2001).

COGNITIVE AND LEARNING THEORIES OF ANXIETY DISORDERS

The investigation of cognitive abilities in patients with AD has attracted increasing interest in the last decades. A great deal of clinical research has been directed toward a better understanding of mechanisms underlying changes in explicit and autobiographical memory in highly anxious individuals and patients with AD. These studies have been considerably influenced by cognitive theories of AD (Clark, 1999; Clark and Beck, 2010).

A central element of cognitive theories of AD is the proposition that the negative beliefs and covert cognitive avoidance behavior associated with AD are a result of the patient's misinterpretation of internal and external stimuli (e.g., the behavior of other individuals, fear associated stimuli from the environment, interoceptive physical sensations, and/or mental events) as being highly dangerous (Bouton et al., 2001; Mathews and MacLeod, 2005). Furthermore, avoidance behavior is maintained because anxiety patients tend to selectively retrieve (personally relevant) information from the past, and in particular those information, which confirm their negative interpretation of current or anticipated situations (Clark, 1999). Likewise, learning theories emphasize the importance of analyzing personally relevant autobiographical memories in anxiety patients (e.g., Öst and Hugdahl, 1981). The examination of the patient's retrospective memory can reveal the fear conditioning events that have led to the disorder and help to explain the development of negative beliefs and avoidance behavior in these individuals (Öst and Hugdahl, 1981).

THE RELATION OF AUTOBIOGRAPHICAL AND EPISODIC MEMORY RETRIEVAL AND ANXIETY-RELATED SYMPTOMS

One possible factor that potentially contributes to the maintenance of negative beliefs, maladaptive emotional responses, and avoidance behavior is the dysfunctional retrieval of past experiences from autobiographical and episodic memory (Clark, 1999; Mathews and MacLeod, 2005). It is proposed that AD patients tend to explicitly re-experience past phobic experiences when confronted with the phobic stimulus, which in turn potentiates the fear responses (Fehm and Margraf, 2002; de Quervain and Margraf, 2008). Since exposure to the phobic stimulus is the rationale of exposure-based therapies in AD excessive retrieval of aversive multimodal memories may be even disadvantageous in the context of such an intervention. Therefore, the modulation and interruption of this "vicious circle" is a major focus of novel approaches in the

optimization of exposure-based treatments (Fehm and Margraf, 2002; de Quervain and Margraf, 2008).

In contrast to biased retrieval of highly emotional events and stimuli in AD, a growing body of evidence, for instance from neuropsychological investigations, has shown that individuals with clinical levels of anxiety exhibit impaired episodic memory for neutral, emotionally irrelevant information (Airaksinen et al., 2005). These findings suggest that specific characteristics in the storage and retrieval of episodic memory in AD depend on the emotional valence of the processed information. The assessment of everyday's episodic memory in the course of AD pathology can provide important clues on the patient's level of cognitive functioning. Normal cognitive functioning is a prerequisite for a number of therapeutic interventions, including cognitive behavioral therapy, and could also be used as an indicator of treatment prognosis and guidance for treatment planning (Tabarés-Seisdedos et al., 2008; Mur et al., 2009).

In sum, a great deal of evidence suggests that highly anxious individuals and patients with AD show systematic changes in explicit and/or episodic memories. However, a closer inspection of the literature reveals several methodological and conceptual issues regarding the definition and measurement of episodic memories, which makes the interpretation of current findings difficult.

REVIEW OUTLINE

The outline of this review is as follows: first, we discuss the different methods and definitions used to operationalize episodic memory. This enables us to provide a working definition of episodic memory that captures the core elements of the concept and that can be used in clinical studies. Based on this, we will provide a brief critical review of the current state of research on the changes in episodic memories in highly anxious individuals and patients with different AD, i.e., PD, specific phobia, social phobia, PTSD, GAD, and OCD. We will also give an update on studies investigating the neurobiological underpinnings of episodic memory functions in the context of AD. Finally, we will discuss the significance of current episodic memory research for the etiology and treatment of AD.

Our overview is based on evidence accumulated from two major lines of research: (i) studies assessing explicit and autobiographical memories for emotionally loaded and/or disorder congruent information and (ii) investigations on episodic memories for neutral information (as revealed predominantly in the context of neuropsychological investigations) in different AD and highly anxious individuals. Whereas a comprehensive overview of the findings is beyond the scope of this review and can be found elsewhere (McNally, 1997; Coles and Heimberg, 2002; Williams et al., 2007; Mitte, 2008), our central aim is rather to draw conclusions from the findings on the interplay between episodic memory and anxiety. We will delineate that, due to methodological and conceptual issues, current research on episodic memory in clinical settings is still inconclusive. In order to produce meaningful results, clinical research should integrate recent methodological and conceptual refinements from the field of behavioral neuroscience (e.g., Kinugawa et al., 2013; Pause et al., 2013, this research topic; Pause et al., 2010). A more systematic research of episodic memory in AD will be valuable to increase our understanding of the core pathology and mechanisms underlying successful treatment of AD.

THE CONCEPT OF EPISODIC MEMORY: PAST AND PRESENT

Before summarizing previous findings on episodic memory functions in anxiety, it is essential to dissect the definition of episodic memory and how the concept of episodic memory, coined by Endel Tulving in the early 1970s (Tulving, 1972), has gradually changed and extended during the last decades (Squire, 2004).

PubMed search using the key words "episodic memory" yielded more than 6200 hits. A careful examination of this literature revealed that there is still no common consensus on the most important core elements of episodic memory and how it should be measured. In fact, numerous working definitions of episodic memory have been proposed. Unfortunately, they are very divergent and sometimes contradictory.

In the early 70s, Tulving (1972) introduced the concept of episodic memory as a system that receives and stores multimodal information about past personal events and their spatial and temporal context. More recent definitions postulate that EM is associated with autonoetic awareness, which describes a feeling that one is remembering something that has happened to oneself, is not happening presently, and is part of one's personal history (Tulving, 2002; Hampton and Schwartz, 2004; Suddendorf and Corballis, 2007).

Humans are using past experiences (episodic memory) to anticipate future events and plan their actions in these imagined scenarios (prospective memory). Thus, an important extension of the initial definition of episodic memory was that episodic memory is not only concerned with the recollection of past experiences, but also implies one's capability to imagine or pre-experience events, which may potentially happen in the future (Harris, 1984; Atance and O'Neill, 2001). The latter is referred to as episodic future thinking or prospective memory (Brandimonte et al., 1996).

Most importantly, both subsystems co-exist within the episodic memory system. For example, we remember engaging in a certain action (e.g., meeting a friend in a bar) at a specific place and time (retrospective memory), but we are also likely able to remember to initiate the same action again at a specific time-point within a spatially well-defined location (e.g., meeting another friend in a cafe). Findings from various lesion, pharmacological, and neuroimaging studies implicate that the brain structures mediating retrospective and prospective episodic memory processes are closely linked (Addis et al., 2007). The medial prefrontal cortex and the posteromedial parietal cortex as well as the medial temporal lobes seem to represent the most critical structures for these processes (Addis et al., 2007; Szpunar et al., 2007).

EXPLICIT MEMORY BIAS IN ANXIETY DISORDERS

As outlined above, a great deal of research on amnestic functions in patients with AD was conducted to test the predictions made by cognitive theories of AD (Bower and Cohen, 1982; Beck et al., 1985; Mogg et al., 1987; Bradley et al., 1995). Although these theories are grounded on marginally different models, they all proposed an enhanced implicit and/or explicit retrieval (defined as implicit/explicit memory bias) of disorder-specific information as a crucial factor contributing to the maintenance of anxiety

pathology. In other words, patients with AD are more likely to retrieve memories that contain disorder-relevant threatening content as compared to memories bearing disorder-irrelevant neutral or positively valenced contents. In **Table 1** studies on explicit memory bias in different AD and their major findings are summarized according to the sample characteristics, diagnostic method, and stimulus materials used.

EXPLICIT MEMORY BIAS IN PANIC DISORDER AND AGORAPHOBIA

The first studies that aimed to test the hypothesis of an explicit memory bias were performed with patients diagnosed with PD and agoraphobia (see Bower and Cohen, 1982; Nunn et al., 1984). According to DSM-5, PD is characterized by unexpected attacks of fear and anxiety, which in some cases (although not necessarily, see Margraf and Ehlers, 1989) are accompanied by strong activation of the sympathetic nervous system. Panic attacks often become chronic and can occur without clearly identifiable causes (triggers) or on occasions where escape and/or help from other persons would be difficult to obtain (the latter being diagnosed as PD with agoraphobia). PD with and without agoraphobia are believed to be based on biological and psychological processes as well as on psychophysiological interactions (Margraf et al., 1986a; Margraf and Ehlers, 1989; McNally, 1990).

In an early investigation by Nunn et al. (1984), patients with PD and agoraphobia and normal controls were instructed to recall text passages containing both, neutral as well as panic-related material. In a subsequent test performed 5 min later, agoraphobic patients recalled more propositions from the panic-related passages as compared to normal controls. This finding was replicated in a subsequent test where agoraphobic patients and controls had to recall threatening and neutral words (Nunn et al., 1984). Again, a superior retrieval of threat-related words relative to neutral words was found in agoraphobic patients. These findings are in line with cognitive and learning theory models of AD, which assume that agoraphobic patients show increased attention to interoceptive physical perceptions while the patient's interpretation and evaluation of these perceptions is (at least partially) guided by the retrieval of episodic memories of panic-associated, threatening events (Margraf et al., 1986a,b; Margraf and Ehlers, 1989; Zucker et al., 1989; McNally, 1997; Clark, 1999).

Later on, several studies investigated whether patients with PD and agoraphobia would show an explicit memory bias for threatening and panic-related material (see **Table 1**). These studies typically employed experimental tasks where anxiety patients and healthy participants were instructed to memorize verbal items that were either neutral or contained threatening and/or panic-relevant information. It was found that PD patients exhibit superior recall and recognition of anxiety words (McNally et al., 1989), panic-associated words (Cloitre and Liebowitz, 1991; Becker et al., 1994, 1999; Pauli et al., 2005), socially relevant words (Beck et al., 1992), and physical-threat-related words (Lundh et al., 1997) when compared with healthy, non anxious controls. However, there are also negative findings in the literature (e.g., Pickles and van den Broek, 1988) as well as studies that suggest that the explicit memory bias in PD is highly dependent on the verbal material used (Becker et al., 1994). Becker et al. (1994) investigated the explicit memory bias in PD patients by using learning material that consisted of pleasant, unpleasant, and PD-related words. Here, patients with PD and normal controls were instructed to memorize these three categories of words and to image a specific, personal scene for each word. After the patients and controls had performed a tactile distractor task, explicit memory for the study items was probed with a free-recall test. While the number of correctly remembered positive and negative words was comparable between groups, PD patients recalled more PD-related words than controls.

EXPLICIT MEMORY BIAS IN POST-TRAUMATIC STRESS DISORDER, SPECIFIC PHOBIA, AND SOCIAL PHOBIA

Similar to the results obtained in PD, findings on explicit memory bias in PTSD have been relatively consistent (see **Table 1**). For example, by using both free and cued recall tests war veterans who had developed PTSD showed an explicit memory bias for combat words (Zeitlin and McNally, 1991; Vrana et al., 1995). Likewise, PTSD patients, who have experienced quite different types of traumatic events, including crime victims (Paunovi et al., 2002) and Holocaust survivors (Golier et al., 2003), have shown an enhanced processing and retrieval of trauma-related words. In contrast to these findings, however, a number of studies consistently reported poorer explicit memory for disorder-irrelevant information in PTSD patients (reviewed in Isaac et al., 2006; Brewin et al., 2007). These findings suggest that explicit memory alterations in PTSD are not global, affecting both trauma-related and -unrelated material. Moreover, the changes are also not unidirectional (only improvement or impairment of memory), but rather highly selective for the type of learning material (but see also section on "Episodic Memory for Neutral Information in Anxious Individuals and Patients with Anxiety Disorders").

With respect to explicit memory bias in other phobias, studies were predominantly performed with patients suffering from social or spider phobia. For spider phobia, the results are rather mixed as some studies found an enhanced retrieval of spider-related material (Rusted and Dighton, 1991; Watts and Coyle, 1992) while other studies showed opposite findings (Watts and Dalgleish, 1991) or reported similar performance between spider phobic and non-phobic individuals (Thorpe and Salkovskis, 2000).

The majority of studies found no evidence for an explicit memory bias for social-threat stimuli in people with social phobia or a high level of social anxiety (e.g., Rapee et al., 1994; Cloitre et al., 1995; Lundh and Öst, 1997; Brendle and Wenzel, 2004; Rinck and Becker, 2005; Wenzel et al., 2005; see **Table 1**). Biased retrieval in social phobia was investigated predominantly by using verbal stimuli (Coles and Heimberg, 2002), which might represent a major reason for the low number of positive results. In fact, some researchers noted that it might be more beneficial to use facial expressions of emotions instead of words to study cognitive biases in social phobia, because facial expressions of emotions in particular are the social cues by which social phobia patients are "captured" (Foa et al., 2000; Chen et al., 2002; Pishyar et al., 2004). Foa et al. (2000) provided evidence that participants with generalized social anxiety indeed show a better overall memory for facial expressions compared to non-anxious controls, but also exhibit an enhanced recognition of negative faces compared to positive

Table 1 | Diagnostic methods and findings from studies assessing episodic memory for emotional and/or disorder-related material in different AD.

Disorder	Sample characteristics	Diagnostic method(s)	Stimulus material	Memory effect(s)	Reference
PD and agoraphobia	PD patients and agoraphobia vs. controls	Free recall	Panic-related vs. neutral passages or threatening vs. neutral words	Enhanced memory for panic-related passages and threatening words in PD	Nunn et al. (1984)
			Anxiety-, panic-, social-, physical-threat words	Enhanced memory for all word types in PD	McNally et al. (1989), Becker et al. (1994), Becker et al. (1999), Cloitre and Liebowitz (1991), Beck et al. (1992), Lundh et al. (1997)
	PD patients vs. controls	Free recall	PD-related vs. pleasant vs. unpleasant words	Enhanced memory for PD-related words in PD	Becker et al. (1994)
		Recognition	Panic-relevant vs. neutral words	Enhanced discrimination and faster reaction times for panic words in PD	Pauli et al. (2005)
	PD patients vs. GAD patients vs. controls	Free recall	Threatening vs. neutral passages or words	No between-group effects	Pickles and van den Broek (1988)
PTSD	Crime victims with acute PTSD vs. controls	Free recall	Trauma-related vs. positive and neutral words	Enhanced memory for trauma-related words in PTSD	Paunovi et al. (2002)
	Holocaust survivors with vs. without PTSD vs. controls	Paired associate recall	Holocaust-related vs. neutral words	(a) Enhanced recall of Holocaust-related words in PTSD (b) Poorer paired associate recall in PTSD	Golier et al. (2003)
	War veterans with vs. without PTSD	Free recall; recognition	Combat words (specific or general), other trauma-related vs. neutral words	Enhanced memory for emotional words in PTSD	Vrana et al. (1995)
		Cued recall	Combat, social-threat, vs. positive and negative words	Impaired memory for all word categories in PTSD except for combat words	Zeitlin and McNally (1991)
Specific phobia	Spider phobics vs. controls	Recall	Spider-related vs. neutral words	(a) Enhanced memory in spider phobics (b) Impaired memory in spider phobics	Rusted and Dighton (1991), Watts and Coyle (1992) Watts and Dalgleish (1991)
	Spider phobics vs. other specific phobia vs. controls	Free recall; recognition	Video clips of spiders	No group difference on recall or recognition	Thorpe and Salkovskis (2000)
Social Phobia (SP)	High social anxiety vs. low social anxiety	Face recognition	Happy vs. angry faces	(a) No effect on recognition in high social anxiety (b) Enhanced recognition for happy faces in low social anxiety	D'Argembeau et al. (2003)
		Recall	Positive social vs. negative social vs. neutral passages	No group effect of stimulus material on recall	Brendle and Wenzel (2004)
			Positive, negative vs. neutral video vignettes		Wenzel et al. (2005)
		Cued recall	Positive vs. neutral vs. social-threat vs. physical-threat words		Lundh and Öst (1997)

(Continued)

Table 1 | Continued

Disorder	Sample characteristics	Diagnostic method(s)	Stimulus material	Memory effect(s)	Reference
	Social phobics vs. controls	Face recognition	Critical vs. accepting faces	(a) Overall enhanced memory for faces in social phobia (b) Enhanced memory for critical faces in social phobia	Lundh and Öst (1996), Foa et al. (2000), Coles and Heimberg (2005)
				(c) Overall impaired memory for faces in social phobia	Pérez-López and Woody (2001)
	Social phobia patients, high social anxiety vs. controls	Free recall	Social phobic vs. neutral verbal stimuli	Enhanced recall for affectively valenced words (positive and threat) in all groups	Cloitre et al. (1995), Lundh and Öst (1997), Rapee et al. (1994), Rinck and Becker (2005)
GAD	GAD vs. SP vs. controls	Free recall	GAD-relevant vs. social anxiety-relevant vs. pleasant vs. neutral words	(a) No group effect (b) Better recall for positive words in all groups	Becker et al. (1999)
	GAD vs. depressed vs. controls		Anxiety-relevant vs. depression-relevant vs. positive vs. neutral words	(a) Enhanced recall of depression-relevant words in depressed patients (b) No effect of stimulus material for GAD patients	Bradley et al. (1995)
	GAD vs. controls	Recognition	Threat-relevant vs. neutral words	(a) No group effect (b) More recognition of threat-words in both groups	MacLeod and McLaughlin (1995)
		Free recall	Ideographically selected threat words	Enhanced recall of thread words in GAD	Coles et al. (2007)
OCD	OCD patients (with contamination fears) vs. anxious and healthy controls	Free recall	Contaminated vs. clean objects	(a) Enhanced recall of contaminated objects in OCD (b) No group effect on recall of which tissue has touched the objects	Radomsky and Rachman (1999)
	OCD (wash) vs. OCD (checking) vs. socially anxious patients vs. healthy controls			(a) No group effect for recall of contaminated objects (b) Enhanced recall of which tissue has touched the objects	Ceschi et al. (2003)
	OCD patients with checking behavior vs. controls		Threat-relevant vs. neutral actions	Enhanced recall of previously experienced threat-relevant actions in OCD	Constans et al. (1995)
	OCD patients vs. controls	Directed forgetting paradigm; free recall; recognition	Negative vs. positive vs. neutral words	Impaired ability to forget negative words in OCD	Wilhelm et al. (1996)
	OCD patients vs. anxious and non-anxious controls	Free recall; confidence ratings	Safe vs. unsafe. vs neutral objects	(a) No group effect for memory accuracy (b) Decreased confidence for unsafe objects over trials in OCD	Tolin et al. (2001)
	OCD patients vs. subclinical checkers vs. controls	Initial-cued recall; confidence ratings; recognition	Threat-relevant vs. neutral word pairs	(a) Impaired recognition and recall in OCD patients (b) Less confidence about future memory performance in OCD (c) No group effect for threat-relevant stimuli	Tuna et al. (2005)

faces (see also Lundh and Öst, 1996; Coles and Heimberg, 2005; for similar results). However, it should be noted that several subsequent studies failed to replicate the findings of Foa et al. (2000) and demonstrated no differences in the recognition and recall of threatening faces between socially anxious and non-anxious persons (e.g. D'Argembeau et al., 2003; reviewed in Staugaard, 2010). Furthermore, a poorer memory for facial expressions in socially anxious participants compared to healthy controls was also demonstrated (Pérez-López and Woody, 2001). Hence, irrespective of the methodological approach, a conclusion on possible memory biases for threatening information in social phobia is still not possible and continues to be a matter of extensive research (see Staugaard, 2010; LeMoult and Joormann, 2012).

EXPLICIT MEMORY BIAS IN GENERALIZED ANXIETY DISORDER AND OBSESSIVE–COMPULSIVE DISORDER

Given the complexity of GAD, it is not surprising that most studies failed to find an explicit memory bias toward threat-related material in GAD patients (e.g., Bradley et al., 1995; MacLeod and McLaughlin, 1995; Becker et al., 1999; reviewed in Coles and Heimberg, 2002). For instance, among other methodological factors, negative findings might be due to the difficulty of finding specific, disorder-relevant trigger stimuli, associated with the GAD patient's individual domain of worries (see Coles et al., 2007). Coles et al. (2007) used verbal material with individually selected words of personal relevance to the patient's worry domain and showed that GAD patients tend to exhibit an explicit memory bias, i.e., a superior recall of threatening words as compared to neutral words.

Compared to other AD, little research exists on explicit memory bias in OCD. The majority of the studies so far, found a bias in explicit memory for disorder congruent word-material in OCD patients (see **Table 1**) although conflicting results had also been reported (e.g., Tuna et al., 2005). Radomsky and Rachman (1999) reported a better memory for contaminated than for clean stimuli in OCD patients, but not in healthy and anxious controls with comparable memory abilities. In line with these results, Constans et al. (1995) reported that OCD patients with checking rituals showed an enhanced recall of previously experienced threat-related actions as compared to non-anxious participants. In another study, neutral, positive, and negative words were presented to OCD patients with different compulsions and obsessions (Wilhelm et al., 1996). In the context of a directed forgetting paradigm, OCD patients recalled more of the negative words that they were told to forget than neutral words assigned with the forget instruction (Wilhelm et al., 1996). Tolin et al. (2001) used a somewhat different approach and presented objects classified as safe, unsafe, or neutral by the participating OCD patients. In a subsequent memory test, the OCD patients, anxious and non-anxious controls were asked to recall as many of these objects as possible and to state the level of confidence in their memories. Although no differences in the recalled number of objects between the three groups were found, the confidence for the same unsafe objects decreased across trials in the group of OCD patients. In a subsequent study using a larger group of OCD patients and more specific controls, Ceschi et al. (2003) showed that OCD patients with washing and cleaning compulsions did not remember more dirty than clean objects when instructed to recall them freely. However, OCD patients showed a memory bias when asked if an object had been touched with a clean or dirty tissue, as they more often recalled the dirty tissue touching the object. It should be noted that the interpretation of these findings is relatively difficult since OCD is also associated with relatively profound deficits in executive functions (Bannon et al., 2006).

EXPLICIT MEMORY BIAS IN ANXIETY DISORDERS: SUMMARY AND INTERPRETATION

In a recent meta-analysis of studies investigating implicit and explicit memory bias in clinically anxious patients and non-clinical samples, effect sizes across all studies point toward a better explicit memory recall of threatening material in patients with AD relative to non-anxious and/or low-anxious controls (Mitte, 2008). Nevertheless, as reviewed above, the evaluation of explicit memory biases in AD is a complex research question and several methodological differences need to be taken into account when interpreting the results. The results are mixed and/or there is little evidence available to draw a definitive conclusion. Furthermore, several factors seem to modulate or even confound the observed effects. The magnitude of the explicit memory bias in anxiety populations is highly dependent on the encoding and retrieval procedure, but also on the time interval interposed between the encoding and recall phase (see Coles and Heimberg, 2002; Mitte, 2008). Most importantly, however, most of the studies conducted so far used words or other verbal stimuli like sentences or stories to study the explicit memory bias in AD (Mitte, 2008). In this regard, it was questioned whether verbal learning leads to cognitive biases to the same extent in different AD (e.g., Wenzel and Holt, 2002; Pishyar et al., 2004). While text passages might induce a more elaborative processing than single words in some AD (Wenzel and Holt, 2002), it certainly would be worth investigating whether explicit memory bias could be reliably replicated when using real-life objects and pictorial material (e.g., information from real-life situations and/or social interactions) as learning stimuli (but see Foa et al., 2000). Although the current discrepancies between studies might be due to the specific nature and the severity of the particular AD, it is also likely that the results are highly dependent on the kind of tasks used to measure explicit memory. This question is of special importance when we consider findings of explicit memory bias in AD as proof of alterations in episodic memory (but see Section "The Need for Novel Episodic Memory Tests in the Clinics").

OVERGENERALIZED AUTOBIOGRAPHICAL MEMORIES AND BIASED RETRIEVAL OF AUTOBIOGRAPHICAL CONTENT IN ANXIETY DISORDERS

Autobiographical memory is another important memory domain that is conceptually related to episodic memory and has been investigated in emotional disorders. The increasing interest of clinical psychologists in autobiographical memory evolved primarily from reports of overgeneralized autobiographical memory (OGM) in patients with major depression. OGM refers to problems in recalling and reporting on temporally and spatially specific events of one's own personal past.

Up to now, autobiographical memory has been mainly assessed with the Autobiographical Memory Test (AMT), introduced by

Williams and Broadbent (1986). In the AMT, participants are instructed to describe specific memories in response to cue words with different valences. As part of the instructions, participants are told that the remembered episode should be an outstanding event, which happened on a particular day and took place at a certain location. Reported memories are coded with regard to their specificity by an independent rater. Only when the participants provide information about the time and the particular place of the reported event, it is rated as a specific memory. In contrast, if participants report more generic personal memories based on repeated experiences or entire periods in their lives, these memories are classified as OGM. However, it is important to note that most versions of the AMT involve response-time limits of 30 or 60 s and that omissions are in some cases added to the OGM score (Van Vreeswijk and de Wilde, 2004; Griffith et al., 2012). Therefore, one has to consider that any physiological process or pathology involving slowing of reaction times or response latencies can confound the measurement in this task. Aged individuals or persons suffering from a depressive episode as well as patients using anxiolytic drugs are expected to have longer reaction times and response latencies.

Williams and Broadbent (1986) were the first to delineate the relation between psychopathology and OGM. In their seminal study, suicidal patients retrieved autobiographical events in a more general mode as compared to clinical and healthy controls. Later on, Williams et al. (1996) extended their initial findings and demonstrated that compared to controls, suicidal depressed patients also anticipate future events with a similar lack of episodic specificity.

OVERGENERALIZED MEMORIES IN MAJOR DEPRESSION AND POST-TRAUMATIC STRESS DISORDER

Overgeneralized autobiographical memory was proved to be a relatively stable characteristic of patients with a major depression. A higher level of OGM has been proposed to be a risk factor that increases the chance to develop major depression (Rawal and Rice, 2012), and is predictive of an unfavorable prognosis (see meta-analysis by Sumner et al., 2010).

The OGM effect is not restricted to individuals with major depression. There is also substantial evidence for OGM in patients with a PTSD (McNally et al., 1994, 1995; Moore and Zoellner, 2007; Sutherland and Bryant, 2007, 2008a; Moradi et al., 2012), cancer survivors (Kangas et al., 2005), and injured individuals with acute stress disorder (Harvey et al., 1998; see **Table 2** for summary). Brown et al. (2013) recently demonstrated that PTSD patients show similar deficits in memory specificity when generating future events. However, it should be noted that to date there is no evidence for a causal relationship between OGM and the etiology of major depression and/or PTSD. Nevertheless, it has been proposed that by being overgeneral, patients with emotional disorders might try to avoid the conscious processing of highly emotional material associated with negative personal experiences (Williams et al., 2007). In particular, since the remembrance of specific aversive experiences often evokes mental images, physical symptoms, and negative emotions (Hermans et al., 2006), the retrieval of less specific/detailed memories may be a coping strategy that protects against negative affects (Hermans et al., 2006; Williams et al., 2007). This type of aversive-memory manipulation qualifies as a cognitive avoidance behavior that is associated with a negative long-term outcome: patients continue to maintain impaired affect regulation and show an increased vulnerability for future depressive and anxiety symptoms (Hermans et al., 2006; Kleim and Ehlers, 2008; Watkins, 2008).

However, it should be noted that apart from PTSD, studies conducted in patients with other AD could not demonstrate an OGM (Burke and Mathews, 1992; Wenzel et al., 2002, 2004; Wenzel and Cochran, 2006; Heidenreich et al., 2007). The presence of a full-blown major depression, as a comorbid factor, or at least some depressive-like symptoms, rather than the AD itself, might be the critical factor that possibly determines whether or not OGM are evident in a given disorder (Wilhelm et al., 1997; Wessel et al., 2001; Williams et al., 2007).

BIASED AUTOBIOGRAPHICAL MEMORY IN ANXIETY DISORDERS

In sum, the data reviewed so far suggest that AD are not directly associated with OGM. To the contrary, there is some evidence indicating that some AD (i.e., PD, specific and social phobia) are characterized by a biased recall of autobiographical memories (see **Table 2**). In particular, it has been shown that PD patients exhibit a threat-relevant memory bias for autobiographical events. This bias is indicated by a more rapid retrieval and a more accurate reproduction of the content of threat-relevant material after being cued with PD-related thoughts (Wenzel and Cochran, 2006). Likewise, there is some evidence that socially anxious individuals show an enhanced memory of threatening and highly emotional autobiographical material (Wenzel and Cochran, 2006; Krans et al., 2013; reviewed in Morgan, 2010), which is being discussed as a core feature of the psychopathology in social anxiety (Morgan, 2010). Finally, it has been shown that spider- and blood/injury-fearful individuals exhibit an enhanced retrieval of negative autobiographical memories and show a greater specificity in the recall of episodes containing direct encounters with the feared stimuli (Wenzel et al., 2003).

AUTOBIOGRAPHICAL MEMORY BIAS AND OVERGENERALIZED MEMORIES IN ANXIETY DISORDERS: SUMMARY AND DISCUSSION

Overall, the literature on autobiographical memory function in AD is still inconclusive and certainly more research on this issue is needed. Some evidence is available for biases in autobiographical memory, but the results are mixed and are exclusively derived from patients with PD and specific or social phobia. Prior to a final evaluation of these studies, it is necessary to briefly discuss the pitfalls and drawbacks of the methods used in these studies. Most of the findings so far have been obtained with the AMT. While the AMT is a gold standard in research, in a recent review by Griffith et al. (2012), the authors list numerous critical issues, all of which can contribute to differences in the calculation and interpretation of AMT scores. According to this review it can be concluded (see Griffith et al., 2012 for more details) that several pitfalls listed below might have led to misleading results in the existing research literature: (I) the execution of the AMT is not standardized and differs across various studies. For example, cue words are presented orally, visually, both orally and visually, or in written form, sometimes by

Table 2 | Findings on OGM and biased autobiographical memory in AD as assessed by different versions of the autobiographical memory test.

Disorder	Sample characteristics	Material	Memory effect(s)	Reference
PTSD	Vietnam combat veterans with PTSD vs. with other disorders vs. without other disorders	Combat-relevant vs. neutral videotape and positive, neutral, and negative cue words	OGM especially after combat-relevant videotapes in PTSD	McNally et al. (1994)
	Veterans with vs. without PTSD vs. controls	Trauma-related vs. positive cue words	(a) OGM in PTSD: fewer specific memories in PTSD than in veterans without PTSD and controls (b) Fewer specific memories in veterans without PTSD than in controls	Moradi et al. (2012)
	Injured individuals with vs. without acute stress disorder (ASD)		(a) OGM for positive cues in ASD (b) Correlation with PTSD symptom severity at a 6 months follow-up	Harvey et al. (1998)
	Patients with vs. without ASD after cancer diagnosis		OGM in patients with ASD	Kangas et al. (2005)
	PTSD vs. trauma-exposed non-PTSD individuals	Positive vs. negative cue words	OGM in PTSD regardless of cue valence	Sutherland and Bryant (2008a)
			More trauma-related memories in response to positive cues	Sutherland and Bryant (2008b)
	PTSD patients		Symptom improvement after cognitive behavioral therapy associated with improved retrieval of specific memories in response to positive cues	Sutherland and Bryant (2007)
	Combat veterans with vs. without PTSD	Neutral cue words	(a) OGM in PTSD (b) Overgeneral future imaging in PTSD	Brown et al. (2013)
Various anxiety disorders	AD with a history of major depression vs. AD and major depression in remission vs. AD and current major depression vs. major depression vs. controls	Positive vs. negative cue words	(a) No OGM in AD patients (b) OGM only in patients with a major depression	Wessel et al. (2001)
GAD	GAD patients vs. controls	Neutral cue words	(a) More and faster recall of anxiety-evoking memories in GAD patients	Burke and Mathews (1992)
Social Phobia (SP)	SP patients with current comorbid depression vs. depression patients without AD vs. controls	Positive vs. negative cue words	No between-group effect on OGM	Heidenreich et al. (2007)
	SP patients vs. controls	Social-threat vs. neutral words	No memory bias toward threat in SP patients	Wenzel et al. (2002)
		Social-threat vs. positive vs. neutral cue words	More retrieval of specific negative memories when cued by social threat in controls	Wenzel et al. (2004)
	High social anxiety vs. low social anxiety	Negative vs. positive cue words	(a) More negative memories in high social anxiety (b) More social anxiety-related memories and more positive memories in response to negative cues in low social anxiety	Krans et al. (2013)

(Continued)

Table 2 | Continued

Disorder	Sample characteristics	Material	Memory effect(s)	Reference
SP and panic disorder (PD)	SP patients vs. PD patients vs. controls	Social phobia-related vs. panic-related vs. control cues	(a) Faster recall of autobiographical memories after social phobia-related cues in SP (b) Faster recall of autobiographical memories after panic-related cues in PD	Wenzel and Cochran (2006)
Specific Phobia	Spider fearful vs. blood/injury-fearful individuals vs. controls	Spider-related vs. blood/injury-related vs. neutral cue words	Increased retrieval of generally negative memories in anxious individuals	Wenzel et al. (2003)
OCD	OCD patients vs. controls	Positive vs. negative cue words	OGM in patients only in the presence of a comorbid MD diagnosis	Wilhelm et al. (1997)

the researcher, sometimes within a computerized version. (II) The word lists used in the AMT were not standardized, but varied across studies in the number of items and word-type, degree of imageability, emotionality, and personal relevance of the retrieval cues. (III) Whether or not response-time limits were applied varied across studies. However, this factor has a profound impact on the way memories are encoded or retrieved. (IV) The interpretation of the AMT results was critically dependent on the study-specific scoring procedure as well as on the handling and scoring of omissions (see also Van Vreeswijk and de Wilde, 2004). Moscovitch et al. (2011) criticized the use of the AMT in the context of social phobia, since the standardized single word cues in the AMT are not sufficient to activate vivid mental images of autobiographical memories in socially anxious participants. Furthermore, the coding system of the AMT might oversimplify the complexity of remembered memories and might subsequently force raters to arbitrarily categorize a reported memory as either specific or general. Moscovitch et al. (2011) proposed that a dimensional approach would be more reasonable since the binary view on specific memories as existent or absent excludes the possibility of measuring partially accessible specific autobiographical memories.

Another important issue that should also be stressed is that a subject's performance in the AMT does not allow conclusions about whether the person accurately recollects his/her previous experiences. In its current form, the AMT does not involve a procedure that probes memory accuracy (Brewin et al., 2010). Moreover, autobiographical experiences are likely to be retrieved and narrated repeatedly, and due to their constructive and dynamic nature, there might be changes in the contents as well as the stability of a memory across time (e.g., due to reconsolidation and interference phenomena, see Schacter et al., 1998; Walker et al., 2003; Earles et al., 2008). Thus, several methodological difficulties are associated with ATM based research, and one should be cautious in drawing the definitive conclusion that autobiographical memory is not affected in a given AD.

EPISODIC MEMORY FOR NEUTRAL INFORMATION IN ANXIOUS INDIVIDUALS AND PATIENTS WITH ANXIETY DISORDERS

While the studies on explicit and autobiographical memory bias stress change in the recall of disorder congruent information in AD, a common secondary finding of these studies is that the recall of neutral or emotionally irrelevant material seems to be largely unaffected in AD. Can we thus conclude that global memory performance, and in particular episodic memory for neutral information, is not affected in clinically anxious people?

Studies on neurocognitive profiles in anxiety patients only partially support this assumption as outlined in the following sections.

EPISODIC MEMORY FOR NEUTRAL INFORMATION IN ANXIETY DISORDERS

An overview of studies, which assessed episodic memory for neutral information in AD is given in **Table 3**. While some studies reported deficits in the recall of neutral verbal information in both social phobia and PD (Lucas et al., 1991; Asmundson et al., 1994; Airaksinen et al., 2005), other studies found no evidence for such impairments in social phobia (Sachs et al., 2004; Sutterby and Bedwell, 2012) and/or PD (Gladsjo et al., 1998; Purcell et al., 1998; Boldrini et al., 2005; see **Table 3**).

Likewise, while extensive research on episodic memory functions has been conducted in patients with PTSD, recent reviews and meta-analysis of the existing literature on episodic, non-trauma-related memory functioning in individuals with PTSD conclude that there is no definite answer to the question (Stein et al., 2002; Neylan et al., 2004; Isaac et al., 2006), or that the association between PTSD and memory impairment appears to be only moderate (Brewin et al., 2007). A series of methodological difficulties arise when interpreting episodic memory functioning in PTSD (see Isaac et al., 2006; Brewin et al., 2007). Memory for emotionally neutral verbal information in PTSD was poorer than the recall for visual stimuli (Vasterling et al., 2002; Brewin et al., 2007). Most importantly, the difficulty of co-morbidity in the patient samples, lack of clear differentiation between PTSD patients who vary with regard to time since trauma, and deficits in attention and executive functions in PTSD (which represent core criteria for the diagnosis of PTSD according to DSM-5), could *per se* have contributed to the findings of impaired episodic memory in PTSD (see Isaac et al., 2006).

Several neuropsychological studies exist in OCD patients (see Greisberg and McKay, 2003 for a review of the literature). While profound deficits in episodic memory functions in OCD were

Table 3 | Diagnostic methods and findings from studies assessing episodic memory for neutral and/or disorder-unrelated material in different AD and highly-anxious individuals.

Anxiety disorder and sample characteristics	Diagnostic method(s) and/or stimulus material	Memory effect(s)	Reference
Population-based sample comprising individuals with PD with and without agoraphobia, social phobia, GAD, OCD, specific phobia vs. healthy controls	Free recall of neutral words	(a) Impaired recall in PD with and without agoraphobia, social phobia, and OCD (b) No effect in GAD and specific phobia	Airaksinen et al. (2005)
PD patients vs. controls	Wechsler Memory Test (WMT); selective reminding; verbal and visual recall	(a) Impaired memory for visual, but not verbal memory in the WMT (b) Impaired recall of verbal and visual items	Lucas et al. (1991)
	Free and cued recall (California Verbal Learning Test; CVLT); visual recognition (Continuous Visual Memory Test; CVMT); Verbal and face recognition (Warrington Recognition Memory Test; WRMT)	(a) No group differences (b) No effect of symptom severity on memory performance	Gladsjo et al. (1998)
PD patients vs. social phobia patients vs. controls	Neuropsychological test battery (verbal learning and memory, visual memory)	(a) Reduced performance in verbal learning and memory in PD and social phobia (b) Inhibited free recall in PD (c) No group effect on visual memory	Asmundson et al. (1994)
Generalized social phobia vs. controls	Verbal and visual immediate and delayed recall of word lists and visual scenes	No group effect	Sutterby and Bedwell (2012)
PTSD patients vs. trauma-exposed individuals vs. healthy controls	Different paradigms for the assessment of episodic memory for neutral information: immediate and delayed verbal recall; visual recognition memory; auditory–verbal recall (Rey Auditory–Verbal Learning Test; RAVL); visuospatial recall; CVLT; different subtests from Wechsler Memory Scale; Visual memory: Rey–Osterrieth Complex Figures Test; ROCF) etc.	Overall mixed results with respect to episodic memory for neutral (verbal and visual) information	Reviewed in Brewin et al. (2007) and Isaac et al. (2006)
OCD patients vs. PD patients vs. depressed individuals vs. controls	Spatial short-term memory (Corsi Blocks); visual memory: recall and recognition	(a) Impaired spatial recognition in OCD (b) No impairments in PD or depressed individuals	Purcell et al. (1998)
OCD patients vs. PD patients with agoraphobia vs. controls	Spatial memory (Corsi Block Tapping Task); verbal memory (Digit Span, Buschke–Fuld Selective Reminding Test)	(a) Impaired verbal memory in OCD (b) Impaired spatial memory in OCD and PD	Boldrini et al. (2005)
OCD patients with checking behavior vs. controls	Digit span test; immediate and delayed recall and recognition etc.	Impaired recall and recognition in OCD	Tallis et al. (1999), Savage et al. (1999), reviewed in Greisberg and McKay (2003)
OCD unmedicated patients vs. controls	ROCF; non-verbal recall	Impaired recall in OCD (depending on symptom severity and regional cerebral blood flow in the right thalamus)	Lacerda et al. (2003)

(Continued)

Table 3 | Continued

Anxiety disorder and sample characteristics	Diagnostic method(s) and/or stimulus material	Memory effect(s)	Reference
OCD patients vs. controls	Word lists; ROCF; free recall and recognition of verbal and visual stimuli (e.g., faces, figures) etc.	(a) Verbal and visual episodic memory impairments (b) Mediation of memory performance by organizational strategies (c) No effect for face recognition	Savage et al. (2000), Penadés et al. (2005) Reviewed in Olley et al. (2007)
OCD patients before vs. after treatment with selective serotonin reuptake inhibitors (4 months)	Non-verbal recall (RCFT)	Improvement of immediate- and delayed-recall after treatment	Kang et al. (2003)
Medicated vs. unmedicated OCD patients	Delayed verbal recall (RAVL); procedural memory (computerized procedural memory test)	No group effect	Mataix-Cols et al. (2002)
GAD patients aged >60 (before and after treatment with escitalopram for 12 weeks) vs. controls aged >60	Immediate and delayed recall of word lists, stories, and figures	(a) Memory impairment in GAD patients before treatment (b) Memory improvement in delayed memory after treatment in GAD patients with low cognitive scores in baseline (c) Strong relationship between anxiety and memory improvement	Butters et al. (2011)

reported (Savage et al., 1999; Tallis et al., 1999; Kang et al., 2003; Kuelz et al., 2004; Boldrini et al., 2005; reviewed in Greisberg and McKay, 2003), negative findings had also been obtained (Mataix-Cols et al., 2002; Bohne et al., 2005). As outlined above, a major factor which may account for the (episodic) memory deficits demonstrated in OCD is a concomitant impairment in executive functions due to frontal lobe dysfunction (Lacerda et al., 2003; Van den Heuvel et al., 2005; Olley et al., 2007). As a consequence, some researchers attempted to dissect the executive component from episodic memory performance in OCD. By using this approach, it was shown that an increased level of organization (in addition to the recall of information) leads to deficits in episodic memory in OCD, whereas the recall of information under controlled and well-organized conditions seems to be unaffected (Savage et al., 2000; Greisberg and McKay, 2003; Penadés et al., 2005). Thus, the memory performance of OCD patients is strongly dependent on task demands. Detrimental effects on episodic memory are more likely to occur in OCD when patients are forced to use organizational strategies during learning (Savage et al., 2000; Greisberg and McKay, 2003; Penadés et al., 2005).

Empirical evidence on episodic memory functions in GAD is relatively scarce (but see Airaksinen et al., 2005). In one of the rare comprehensive evaluations of neurocognitive functions in GAD, deficits in episodic memory (delayed visual and verbal recall) have been reported only for older adults (mean age 71.6 years) diagnosed with GAD (Butters et al., 2011). Interestingly, a 12-week lasting treatment with escitalopram (Cipralex®) improved memory in the delayed verbal memory test in GAD patients with low cognitive scores. In one of the most detailed existing studies, Airaksinen et al. (2005) assessed cognitive functions and specifically episodic memory in population-based samples of persons suffering from an AD. In contrast to other studies, participants were recruited from a population-based sample of persons meeting the DSM-IV criteria for an AD. Overall, their results point toward significant deficits in episodic memory in all subgroups of AD, as measured by both free and cued recall of verbal information. However, episodic memory impairments were more profound in PD and social phobia patients than in any other AD (Airaksinen et al., 2005). The impairment in episodic memory was persistent even when controlling concomitant depressive disorder, alcohol dependence/abuse, or psychopharmacological treatment as covariates. While their outcome somehow suggests that AD indeed have a negative influence on episodic memory functioning (Airaksinen et al., 2005), such a conclusion might be premature, as discussed in the following sections.

THE NEUROANATOMY OF EPISODIC MEMORY IN ANXIETY DISORDERS

Surprisingly, little research has been conducted to identify the neuronal mechanism, which underlies changes in episodic memory functions in the context of an AD. Most of the studies in this field have been conducted in patients diagnosed with PTSD and trauma-exposed subjects without a PTSD diagnosis. By using various imaging techniques [functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)], specific neuronal activation patterns have been described in brain

regions previously associated with episodic memory encoding and retrieval, i.e., the hippocampus, amygdala, and the prefrontal cortex. For example, Brohawn et al. (2010) assessed recognition memory for trauma-related, neutral and positive pictures in PTSD patients and trauma-exposed non-PTSD subjects by using an fMRI approach. They found increased amygdala activation during the encoding of negative (vs. neutral) pictures as well as exaggerated hippocampal activation during recognition of trauma-related pictures in PTSD diagnosed patients. Interestingly, the degree of amygdala activation was positively correlated with current PTSD symptom severity while the amount of hippocampal activation during retrieval was greater in PTSD diagnosed individuals compared to non-PTSD subjects. Dickie et al. (2008) assessed the memory for neutral and fearful face expressions in PTSD patients. They found a negative correlation between the patient's symptom severity (as assessed by Clinically Administered PTSD Scale scores) and memory performance as well as ventral medial prefrontal cortex activity elicited by the subsequently forgotten faces. Similar activation patterns during the storage and retrieval of emotionally loaded episodic memories in PTSD patients have been reported in other studies (Bremner et al., 2003a; Thomaes et al., 2009; Whalley et al., 2009; Hayes et al., 2011). There is also evidence that PTSD patients exhibit a diminished hippocampal activation during encoding (Bremner et al., 2003b), as well as an abnormal regional blood flow response (by using PET) in the hippocampus during the recollection (Shin et al., 2004) of neutral material. In a recent, quite interesting, study by Dickie et al. (2011), changes in neuronal activation during the performance in an emotional face memory encoding task have been reported in patients who recovered from PTSD symptoms. In particular, PTSD patients showing symptom improvement over several months exhibited specific changes in memory-related activations in the hippocampal regions and the subgenual anterior cingulate cortex, suggesting that learning induced neuronal activity might serve as an indicator of PTSD recovery.

To our knowledge, there are only two reports published in which fMRI was recorded in other AD patients during episodic memory performance (Maddock et al., 2003; van Tol et al., 2012). Maddock et al. (2003) demonstrated that patients with PD engage in more intense information processing and deeper encoding when confronted with threat-related stimuli. Most importantly, this increased effort in encoding of threat-related stimuli was associated with higher neuronal activation in the posterior cingulate and dorsolateral prefrontal cortices and with better memory performance for threat-related vs. unrelated stimuli. van Tol et al. (2012) assessed encoding and recognition-associated neuronal activation in AD patients (diagnosed with a PD, social anxiety, and/or GAD), patients with a major depression, comorbid major depression, and healthy controls during an emotional word memory paradigm. Participants were asked to memorize positive, negative, and neutral words and complete a word-recognition task after a short retention interval. Findings from this study point toward a decrease in hippocampal activation during encoding in both patients with major depression and patients diagnosed with an AD. However, specific increase in the activation in the inferior frontal gyrus during the subsequent recognition of previously learned positive material was found exclusively in patients with AD. The observed effects were largely unaffected by medication status and regional brain volume.

Although the evidence available so far is still scarce, findings from neuroimaging studies suggest the presence of a specific and symptom-related activation pattern in brain regions, which are critical for the storage and retrieval of emotionally loaded episodic memories (see Maddock, 1999).

AUTOBIOGRAPHICAL VS. EPISODIC MEMORY: DIFFERENT SIDES OF THE SAME COIN?

The episodic memory system is required for the storage of highly detailed knowledge of past experiences including spatial and temporal context as well as the internal state of the individual during the encoding of the experienced event [including a blueprint of emotions, perceptions, and thoughts in this situation (Dere et al., 2010)]. In contrast, the autobiographical memory system stores parts of the content and context information of an episodic memory and modifies and extends this content information with knowledge from the semantic memory system (reconsolidation–extension phenomenon). In other words, the autobiographical memory system modifies and integrates episodic memories into the individual's biography that take the form of a semantic biographical memory. The important difference between autobiographical and episodic memories is that autobiographical memory can be de-emotionalized, modified, and extended by semantic knowledge in terms of its content (there is evidence that the content of autobiographical memories changes over time with each retrieval–extension–reconsolidation round). Furthermore, it does not necessarily contain a blueprint of the internal state of the individual during encoding and is therefore not associated with a reliving of the experience during recollection as postulated by Tulving (Tulving, 2002; Dere et al., 2010). Thus, autobiographical memories are semantic memories of biographical facts containing some of the information associated with an episodic memory, but are not associated with phenomenological aspects of remembering a past episode (autonoetic awareness), as was originally proposed by Endel Tulving (Tulving, 2002, but see Conway, 2001). Fivush (2011) argues for a developmental distinction of episodic and autobiographical memory. He describes a developmental model where autobiographical memories are built on episodic representations and bind past events together into a personal history. Within this model, autobiographical memories are supposed to act beyond the episodic memory function and represent the central component for guiding current and future behavior (Fivush, 2011). Given these theoretical distinctions between episodic and autobiographical memory, the AMT should not be applied to measure episodic memory function.

AUTOBIOGRAPHICAL VS. VERBAL EPISODIC-LIKE MEMORY: SAME OR DIFFERENT?

The AMT also differs from the assessment of episodic memory through the reproduction of learned lists of items (words, pictures, or faces) in a laboratory setting (Gilboa, 2004; McDermott et al., 2009; Fivush, 2011). The verbal memory test is also not a valid measure of episodic memory function, since it lacks the assessment of the recollection of spatial and temporal information and should be considered as measuring only an episodic-like memory.

The neuroanatomy of verbal episodic-like and autobiographical memory has been reported to be only partially overlapping. There were substantial differences in the neuronal activation patterns between verbal episodic-like memories and autobiographical memories (Gilboa, 2004; Burianova and Grady, 2007; McDermott et al., 2009). Additionally, differences in the temporal dynamics related to the retrieval of autobiographical and verbal episodic-like memory allowed a further distinction between these two memory systems (Conway, 2001).

THE NEED FOR NOVEL EPISODIC MEMORY TESTS IN THE CLINICS

The majority of studies so far used verbal or in some rare cases visual learning to assess episodic memory for emotional and neutral information in AD. It is doubtful whether commonly used tests of episodic memory function are valid measures of episodic memory in a clinical setting (irrespective of whether they rely on the participants' ability to learn words and/or photographs and remember these at a later point via recall, cued recall, or recognition test). One problem raised is that such paradigms measure only one isolated core component of episodic memory, rather than subcomponents (the memory for what, where, and when) and the binding of these components into a unified integrated memory episode according to the definition of episodic memory as a multimodal memory system (see Pause et al., 2010, 2013; Plancher et al., 2010). Verbal learning tests, for example, do not explicitly measure the memory for spatial and temporal context information associated with the learning event, and often there is no spatial and temporal component implicated in the way the verbal memory is tested (Pause et al., 2013). As a consequence, various spatiotemporal memory paradigms have recently been developed, allowing the induction and measurement of the core components of an episodic memory (event, spatial, and temporal information) under experimentally well-defined conditions (Pause et al., 2010; Bellassen et al., 2012; Plancher et al., 2012; Kinugawa et al., 2013).

Other researchers yet suggest that much of what we remember in everyday life refers to visual information embedded in scenes and past actions, and thus emphasize the importance of using ecologically valid episodic memory tasks in a laboratory setting (Piolino et al., 2009; Plancher et al., 2010, 2012). Plancher et al. (2012) used a virtual–reality-based environment in a highly ecological fashion to characterize impairments in episodic memory in amnestic mild cognitive impairment (MCI) and Alzheimer's disease. By using a multimodal approach, the memory for central and perceptual details, spatiotemporal contextual elements, and binding of these elements was assessed in an environment corresponding to real-life experiences (i.e., driving a car through a "virtual" city where different scenes and actions were presented at different locations and at different time-points). The authors found specific episodic memory profiles in amnestic MCI and Alzheimer's disease. Interestingly the patients' daily memory complaints were more highly correlated with the performance in the virtual test than with their performance in the classical neuropsychological memory test.

Irish et al. (2011) investigated episodic memory capacity in amnestic patients with MCI by using a battery of experimental tasks with a high relevance to real-world situations. MCI patients displayed impairments across all domains of episodic memory and particularly in the experimental tasks associated with actions significant in everyday functioning, e.g., remembering faces and names, finding a route, and/or remembering typical daily routine sequences (e.g., getting dressed, traveling to work, the weather that day, see Irish et al., 2011). Thus, it can be argued that episodic memory tests in the laboratory setting can capture core elements of everyday episodic memory and that impairments in specifically designed paradigms in the laboratory can be reliable indicators of changes in everyday episodic memory functions in real-life situations.

As discussed in this section, definite conclusions on possible changes in episodic memory for emotional and neutral information in highly anxious individuals and patients with AD cannot be drawn from the existing literature. We argue that there is still a shortage of studies using valid standardized tests to induce episodic (like) memories and their retrieval (but see Pause et al., 2013) under laboratory conditions. Furthermore, the acceptance of verbal and visual memory tasks as a measure of episodic memory functions largely neglects the complexity of the everyday episodic memory since such tests lack ecological validity and thus cannot provide insights into the individual's level of functioning in real-life situations. There is certainly also the need to develop more reality-based tests that allow a naturalistic assessment of episodic memory in AD that is also useful to monitor changes in response to therapeutic interventions. In this regard, already available virtual reality tests of episodic memory function that have been developed for patients with MCI an Alzheimer's disease could be adapted to AD patients using disease-related and non-related stimuli (Plancher et al., 2012). Of course the test has to be designed in a way that allows repeated administration in order to evaluate the outcome of pharmacological or therapeutic interventions of episodic memory performance or whether fluctuations in symptom strengths are associated with changes in episodic memory performance.

THE SIGNIFICANCE OF THE EPISODIC MEMORY CONCEPT IN THE CONTEXT OF AD

Episodic memory is presumed to have an important evolutionary function, which has remained common across different species (Allen and Fortin, 2013). This unique functional feature of the episodic memory system allows organisms to retrieve spatially and temporally specific information about single, unique experiences (Squire, 2004; Allen and Fortin, 2013). Several lines of evidence show that the retrieval of such spatiotemporal specific experiences is highly relevant for both humans as well as non-human animals (Bluck and Alea, 2002; Dere et al., 2006, 2008).

EPISODIC MEMORIES, PROBLEM SOLVING, AND SELF-EFFICACY

Episodic memory is closely related to the level of functioning in daily life (Irish et al., 2011). In order to initiate adaptive behavior in the present or immediate future, humans, as well as animals, are able to retrieve information encoded during specific events and use these informations to form "memory-based" predictions (Allen and Fortin, 2013). In particular, when faced with current and anticipated problems, one's ability to retrieve specific details from

previous personal events can provide important clues for efficient problem solving (Bluck and Alea, 2002; Williams, 2006; Beaman et al., 2007). Empirical evidence supports the link between episodic memory and problem-solving capacity, i.e., episodic simulation and/or higher specificity in autobiographic memory retrieval is associated with higher effectiveness in problem solving (Brown et al., 2012; Vandermorris et al., 2013). Accordingly, deficits in the specific retrieval of past experiences are highly correlated with poor problem solving (Evans et al., 1992; Sutherland and Bryant, 2008a; MacCallum and Bryant, 2010), which has a clinical impact and is therefore displayed in depressed (Goddard et al., 1996), suicidal (Evans et al., 1992; Pollock and Williams, 2001), and traumatized patients (Sutherland and Bryant, 2008b). However, the underlying cognitive mechanisms of the association between deficits in episodic memory functions and pathological conditions are still a matter of research (Williams, 2006; Williams et al., 2007).

There is also substantial evidence that episodic memory functions have therapeutic relevance and might be directly related to psychological treatment outcome. For instance, one of the core interventions in modern psychological therapies (i.e., cognitive behavioral therapies) for the treatment of mental diseases is to train patients to generate specific skills in order to manage current and future problems. Patients are encouraged to learn to reduce ineffective ways of reacting (e.g., showing avoidance or passivity) and instead react to problems effectively by applying new problem-solving skills (Nezu et al., 2003). The latter can be modified within the therapy context via cognitive restructuring procedures, e.g., realistic goal setting, success visualization, and use of previous negative experiences as a clue to solve present and future anticipated problems (Nezu et al., 2003). The capability to retrieve details from one's own past in a specific way as well as the ability to project oneself into the future and simulate novel events therefore has a potential influence on treatment outcome. Accordingly, instructions aimed at promoting the retrieval of specific positive memories during psychotherapy (i.e., memory specificity training) have recently been associated with greater symptom reduction in older depressed patients (Serrano et al., 2004), adolescents with depression (Neshat-Doost et al., 2013), and inpatients with depressive symptomatology (Raes et al., 2009). Likewise, psychological treatments lead to both symptom improvement and an increased retrieval of specific autobiographical memories in former depressive patients (Williams et al., 2000), patients with complicated grief (MacCallum and Bryant, 2010) as well as PTSD patients (Sutherland and Bryant, 2007). Moreover, Ehlers and Clark (2000) proposed an etiological model of PTSD in which the predictive valence of autobiographical memory capacity for the subsequent development of a PTSD plays a central role (Kleim and Ehlers, 2008). According to this model, successful integration of intrusive traumatic memories into the autobiographical memory base is considered as a critical element for a successful treatment of PTSD (Ehlers and Clark, 2000).

In a very recent study, Brown et al. (2012) suggested that therapy-induced increase in self-efficacy may have a beneficial impact on future directed episodic memory specificity and consequently problem-solving strategies. In their experimental work, they examined whether manipulating self-efficacy in healthy students has an impact on the capacity to recall the past and imagine one self in the future (mental time travel), and whether such manipulation can further influence social problem solving. They showed that compared to individuals in the low self-efficacy group, individuals in the high self-efficacy group generated past and future events with greater specificity and also performed better on social problem-solving indices. It should be noted that the majority of studies on clinical significance of episodic memory functions deal with affective disorders. Apart from PTSD (Sutherland and Bryant, 2007, 2008a), evidence for an association between therapy-induced symptom reduction, problem-solving capacity and episodic memory specificity in AD requires empirical confirmation.

EXCESSIVE RETRIEVAL OF AVERSIVE EXPERIENCES IN THE CONTEXT OF EXPOSURE-BASED TREATMENTS

Different lines of evidence suggest that the excessive episodic retrieval of aversive experiences may be disadvantageous and may hamper efficacy of psychotherapeutic interventions. Accordingly, the modulation of excessive retrieval (i.e., reducing excessive retrieval) of aversive episodic memories in anxiety patients might represent a mechanism to enhance the effectiveness of exposure-based treatments. Exposure-based treatments arguably represent the most effective form of a psychological intervention in the treatment of AD (Margraf, 2000). However, inter-individual differences in the treatment benefit during exposure-based therapy exist among anxiety patients. For example, a substantial proportion of anxiety patients shows only partial reduction of anxiety symptoms after exposure therapy and/or displays a high incidence of fear relapse phenomena after the completion of the treatment (Heimberg, 2002; Blanco et al., 2003; Davidson et al., 2004; Cottraux, 2005). It is proposed that exposure to a phobic stimulus not only leads to the activation of stimulus-associated fear memory, but is also connected with the retrieval of explicit fearful memories of past phobic experiences, which in turn enhances the fear responses (Lang, 1985; Foa and Kozak, 1986; Cuthbert et al., 2003). In PTSD and specific phobia, excessive retrieval of aversive memories causes re-experiencing symptoms and may reinforce negative beliefs, which may increase the avoidance behavior during exposure therapy (Rapee and Heimberg, 1997; Fehm and Margraf, 2002; de Quervain and Margraf, 2008). Interestingly, psychobiological approaches have recently been developed with the aim to reduce excessive retrieval of aversive memories in patients with AD in the context of an exposure-based treatment (de Quervain and Margraf, 2008). It is demonstrated that glucocorticoid administration during exposure enhances the effectiveness of exposure-based treatments in PTSD and specific phobia (Soravia et al., 2006; de Quervain et al., 2011). The exact mechanisms underlying the beneficial effect of glucocorticoids on exposure therapy benefit remain elusive. However, the administration of glucocorticoids during exposure therapy might modulate fear retrieval and thus interrupt the vicious cycle of spontaneous retrieving, re-experiencing, and reconsolidating of aversive memories in phobic patients leading to a reduction of maladaptive fear responses (de Quervain and Margraf, 2008; de Quervain et al., 2011). Similarly, the narrative exposure therapy (NET) represents an example of a behavioral intervention, which is aimed to selectively change and reorganize

the retrieval of past emotional experiences. NET is a short-term therapy, which is shown to be an effective treatment for PTSD, especially in individuals traumatized by conflict and/or organized violence (Robjant and Fazel, 2010). During NET, PTSD patients are repeatedly exposed to emotional memories of traumatic events and trained to reorganize such high-emotional autobiographical memories into less-emotional coherent chronological narrative. In a typical NET session, patients are asked to narrate stressful life events in a chronological order. Interestingly, it has been shown that patients who are able to form a highly specific and consistent narrative of individual traumatic events benefit most from exposure therapy for PTSD (Foa and Kozak, 1986; Foa et al., 1995; Robjant and Fazel, 2010).

In sum, evidence so far suggests that valuable information on the characteristics of episodic memory alterations in various AD should be taken into consideration when designing and implementing a psychological treatment plan.

CONCLUDING REMARKS

The importance of episodic memories in the context of AD and other mental disorders is increasingly recognized in the last decades. We have discussed several methodological factors that warrant careful consideration in future research on episodic memory functions in clinical populations. We further provided arguments why clinical researchers should incorporate valid paradigms for the assessment of episodic memory functions in order to better understand the pathology and to optimize psychological treatment. The episodic memory system allows the storing and recollecting of emotional experiences and anticipation of potential emotional events in the future. The complexity of everyday episodic memory can thus not be captured through the use of verbal learning tests or other similar standardized memory tests currently used in the clinical setting. Both the recollection of past emotional experiences and the anticipation of future events can affect patient's behavior as well as patient's response to current therapeutic interventions. A major task for psychotherapists and other clinicians is to develop novel research methods and training programs that might help to understand, interpret, and possibly actively use patient's episodic memory to support therapeutic interventions and alleviate the severity and frequency of symptoms. Finally, more research is needed to understand the underlying neuronal basis of episodic memory alterations in AD.

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REFERENCES

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016

Airaksinen, E., Larsson, M., and Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *J. Psychiatr. Res.* 39, 207–214. doi:10.1016/j.jpsychires.2004.06.001

Allen, T. A., and Fortin, N. J. (2013). The evolution of episodic memory. *Proc. Natl. Acad. Sci. U.S.A.* 18, 10379–10386. doi:10.1073/pnas.1301199110

Asmundson, G. J., Stein, M. B., Larsen, D. K., and Walker, J. R. (1994). Neurocognitive function in panic disorder and social phobia patients. *Anxiety* 1, 201–207.

Atance, C. M., and O'Neill, D. K. (2001). Episodic future thinking. *Trends Cogn. Sci.* 5, 533–539. doi:10.1016/S1364-6613(00)01804-0

Bannon, S., Gonsalvez, C. J., Croft, R. J., and Boyce, P. M. (2006). Executive functions in obsessive-compulsive disorder: state or trait deficits? *Aust. N. Z. J. Psychiatry* 40, 1031–1038. doi:10.1111/j.1440-1614.2006.01928.x

Beaman, A., Pushkar, D., Etezadi, S., Bye, D., and Conway, M. (2007). Autobiographical memory specificity predicts social problem-solving ability in old and young adults. *Q. J. Exp. Psychol.* 60, 1275–1288. doi:10.1080/17470210600943450

Beck, A. T., Emery, G., and Greenberg, R. L. (1985). *Anxiety Disorders and Phobias.* New York: Basic Books.

Beck, J. G., Stanley, M. A., Averill, P. M., Baldwin, L. E., and Deagle, E. A. (1992). Attention and memory for threat in panic disorder. *Behav. Res. Ther.* 30, 619–629. doi:10.1016/0005-7967(92)90007-4

Becker, E., Rinck, M., and Margraf, J. (1994). Memory bias in panic disorder. *J. Abnorm. Psychol.* 103, 396–399. doi:10.1037/0021-843X.103.2.396

Becker, E. S., Roth, W. T., Andrich, M., and Margraf, J. (1999). Explicit memory in anxiety disorders. *J. Abnorm. Psychol.* 108, 153–163. doi:10.1037/0021-843X.108.1.153

Bellassen, V., Iglói, K., de Souza, L. C., Dubois, B., and Rondi-Reig, L. (2012). Temporal order memory assessed during spatiotemporal navigation as a behavioral cognitive marker for differential Alzheimer's disease diagnosis. *J. Neurosci.* 32, 1942–1952. doi:10.1523/JNEUROSCI.4556-11.2012

Blanco, C., Raza, M. S., Schneier, F. R., and Liebowitz, M. R. (2003). The evidence based pharmacological treatment of social anxiety disorder. *Int. J. Neuropsychopharmacol.* 6, 427–442. doi:10.1017/S1461145703003791

Bluck, S., and Alea, N. (2002). "Exploring the functions of autobiographical memory," in *Critical Advances in Reminiscence Work: From Theory to Application*, eds J. D. Webster and B. K. Haight (New York: Springer), 61–75.

Bohne, A., Savage, C. R., Deckersbach, T., Keuthen, N. J., Jenike, M. A., Tuschen-Caffier, B., et al. (2005). Visuospatial abilities, memory, and executive functioning in trichotillomania and obsessive-compulsive disorder. *J. Clin. Exp. Neuropsychol.* 27, 385–399. doi:10.1080/13803390490520418

Boldrini, M., Del Pace, L., Placidi, G. P. A., Keilp, J., Ellis, S. P., Signori, S., et al. (2005). Selective cognitive deficits in obsessive-compulsive disorder compared to panic disorder with agoraphobia. *Acta Psychiatr. Scand.* 111, 150–158. doi:10.1111/j.1600-0447.2004.00247.x

Bouton, M. E., Mineka, S., and Barlow, D. H. (2001). A modern learning theory perspective on the etiology of panic disorder. *Psychol. Rev.* 108, 4–32. doi:10.1037/0033-295X.108.1.4

Bower, G. H., and Cohen, P. R. (1982). "Emotional influences in memory and thinking: data and theory," in *Affect and Cognition*, eds M. S. Clark and S. T. Fiske (Hillsdale, NJ: Erlbaum), 291–331.

Bradley, B. P., Mogg, K., and Williams, R. (1995). Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. *Behav. Res. Ther.* 33, 755–770. doi:10.1016/0005-7967(95)00029-W

Brandimonte, M., Einstein, G. O., and McDaniel, M. A. (eds) (1996). *Prospective Memory: Theory and Applications.* Mahwah, NJ: Erlbaum.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Staib, L. H., et al. (2003a). Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol. Psychiatry* 15, 879–889. doi:10.1016/S0006-3223(02)01891-7

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., et al. (2003b). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am. J. Psychiatry* 160, 924–932. doi:10.1176/appi.ajp.160.5.924

Brendle, J. R., and Wenzel, A. (2004). Differentiating between memory and interpretation biases in socially anxious and nonanxious individuals. *Behav. Res. Ther.* 42, 155–171. doi:10.1016/S0005-7967(03)00107-4

Brewin, C. R., Gregory, J. D., Lipton, M., and Burgess, N. (2010). Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. *Psychol. Rev.* 117, 210–232. doi:10.1037/a0018113

Brewin, C. R., Kleiner, J. S., Vasterling, J. J., and Field, A. P. (2007). Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. *J. Abnorm. Psychol.* 116, 448–463. doi:10.1037/0021-843X.116.3.448

Brohawn, K. H., Offringa, R., Pfaff, D. L., Hughes, K. C., and Shin, L. M. (2010). The neural correlates of emotional memory in posttraumatic stress disorder. *Biol. Psychiatry* 68, 1023–1030. doi:10.1016/j.biopsych.2010.07.018

Brown, A. D., Dorfman, M. L., Marmar, C. R., and Bryant, R. A. (2012). The impact of perceived self-efficacy on mental time travel and social problem solving. *Conscious. Cogn.* 21, 299–306. doi:10.1016/j.concog.2011.09.023

Brown, A. D., Root, J. C., Romano, T. A., Chang, L. J., Bryant, R. A., and Hirst, W. (2013). Overgeneralized autobiographical memory and future thinking in combat veterans with posttraumatic stress disorder. *J. Behav. Ther. Exp. Psychiatry* 44, 129–134. doi:10.1016/j.jbtep.2011.11.004

Burianova, H., and Grady, C. L. (2007). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *J. Cogn. Neurosci.* 19, 1520–1534. doi:10.1162/jocn.2007.19.9.1520

Burke, M., and Mathews, A. (1992). Autobiographical memory and clinical anxiety. *Cogn. Emot.* 6, 23–35. doi:10.1080/02699939208411056

Butters, M. A., Bhalla, R. K., Andreescu, C., Wetherell, J. L., Mantella, R., Begley, A. E., et al. (2011). Changes in neuropsychological functioning following treatment for late-life generalised anxiety disorder. *Br. J. Psychiatry* 199, 211–218. doi:10.1192/bjp.bp.110.090217

Ceschi, G., der Linden, M. V., Dunker, D., Perroud, A., and Bredart, S. (2003). Further exploration memory bias in compulsive washers. *Behav. Res. Ther.* 41, 737–747. doi:10.1016/S0005-7967(03)00040-8

Chen, Y. P., Ehlers, A., Clark, D. M., and Mansell, W. (2002). Patients with generalized social phobia direct their attention away from faces. *Behav. Res. Ther.* 40, 677–687. doi:10.1016/S0005-7967(01)00086-9

Clark, D. A., and Beck, A. T. (2010). *Cognitive Therapy of Anxiety Disorders: Science and Practice*. New York: Guilford.

Clark, D. M. (1999). Anxiety disorders: why they persist and how to treat them. *Behav. Res. Ther.* 37, 5–27. doi:10.1016/S0005-7967(99)00048-0

Cloitre, M., Cancienne, J., Heimberg, R. G., Holt, C. S., and Liebowitz, M. R. (1995). Memory bias does not generalize across anxiety disorders. *Behav. Res. Ther.* 33, 305–307. doi:10.1016/0005-7967(94)00051-K

Cloitre, M., and Liebowitz, M. R. (1991). Memory bias in panic disorder: an investigation of the cognitive avoidance hypothesis. *Cognit. Ther. Res.* 15, 371–386. doi:10.1007/BF01173032

Coles, M. E., and Heimberg, R. G. (2002). Memory biases in the anxiety disorders: current status. *Clin. Psychol. Rev.* 22, 587–627. doi:10.1016/S0272-7358(01)00113-1

Coles, M. E., and Heimberg, R. G. (2005). Recognition bias for critical faces in social phobia: a replication and extension. *Behav. Res. Ther.* 43, 109–120. doi:10.1016/j.brat.2003.12.001

Coles, M. E., Turk, C. L., and Heimberg, R. G. (2007). Memory bias for threat in generalized anxiety disorder: the potential importance of stimulus relevance. *Cogn. Behav. Ther.* 36, 65–73. doi:10.1080/16506070601070459

Constans, J. I., Foa, E. B., Franklin, M. E., and Mathews, A. (1995). Memory for actual and imagined events in OC checkers. *Behav. Res. Ther.* 33, 665–671. doi:10.1016/0005-7967(94)00095-2

Conway, M. A. (2001). Sensory-perceptual episodic memory and its context: autobiographical memory. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 356, 1375–1384. doi:10.1098/rstb.2001.0940

Cottraux, J. (2005). Recent developments in research and treatment for social phobia (social anxiety disorder). *Curr. Opin. Psychiatry* 18, 51–54.

Cuthbert, B. N., Lang, P. J., Strauss, C., Drobes, D., Patrick, C. J., and Bradley, M. M. (2003). The psychophysiology of anxiety disorder: fear memory imagery. *Psychophysiology* 40, 407–422. doi:10.1111/1469-8986.00043

D'Argembeau, A., Van der Linden, M., Etienne, A. M., and Comblain, C. (2003). Identity and expression memory for happy and angry faces in social anxiety. *Acta Psychol. (Amst.)* 114, 1–15. doi:10.1016/S0001-6918(03)00047-7

Davidson, J. R., Foa, E. B., Huppert, J. D., Keefe, F. J., Franklin, M. E., Compton, J. S., et al. (2004). Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch. Gen. Psychiatry* 61, 1005–1013. doi:10.1001/archpsyc.61.10.1005

de Quervain, D. J., Bentz, D., Michael, T., Bolt, O. C., Wiederhold, B. K., Margraf, J., et al. (2011). Glucocorticoids enhance extinction-based psychotherapy. *Proc. Natl. Acad. Sci. U.S.A.* 108, 6621–6625. doi:10.1073/pnas.1018214108

de Quervain, D. J., and Margraf, J. (2008). Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach. *Eur. J. Pharmacol.* 583, 365–371. doi:10.1016/j.ejphar.2007.11.068

Dere, E., Kart-Teke, E., Huston, J. P., and De Souza Silva, M. A. (2006). The case for episodic memory in animals. *Neurosci. Biobehav. Rev.* 30, 1206–1224. doi:10.1016/j.neubiorev.2006.09.005

Dere, E., Pause, B. M., and Pietrowsky, R. (2010). Emotion and episodic memory in neuropsychiatric disorders. *Behav. Brain Res.* 215, 162–171. doi:10.1016/j.bbr.2010.03.017

Dere, E., Zlomuzica, A., Huston, J. P., Kart-Teke, E., and de Souza Silva, M. A. (2008). "Animal episodic memory," in *Handbook of Episodic Memory Research*, eds E. Dere, A. Easton, L. Nadel, and J. P. Huston (Amsterdam: Elsevier Science Publishers), 155–184.

Dickie, E. W., Brunet, A., Akerib, V., and Armony, J. L. (2008). An fMRI investigation of memory encoding in PTSD: influence of symptom severity. *Neuropsychologia* 46, 1522–1531. doi:10.1016/j.neuropsychologia.2008.01.007

Dickie, E. W., Brunet, A., Akerib, V., and Armony, J. L. (2011). Neural correlates of recovery from post-traumatic stress disorder: a longitudinal fMRI investigation of memory encoding. *Neuropsychologia* 49, 1771–1778. doi:10.1016/j.neuropsychologia.2011.02.055

Earles, J. L., Kersten, A. W., Curtayne, E. S., and Perle, J. G. (2008). That's the man who did it, or was it a woman? Actor similarity and binding errors in event memory. *Psychon. Bull. Rev.* 15, 1185–1189. doi:10.3758/PBR.15.6.1185

Ehlers, A., and Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behav. Res. Ther.* 38, 319–345. doi:10.1016/S0005-7967(99)00123-0

Evans, J., Williams, J. M. G., O'Loughlin, S., and Howells, K. (1992). Autobiographical memory and problem-solving strategies of parasuicide patients. *Psychol. Med.* 22, 399–405. doi:10.1017/S0033291700030348

Fehm, L., and Margraf, J. (2002). Thought suppression: specificity in agoraphobia versus broad impairment in social phobia? *Behav. Res. Ther.* 40, 57–66. doi:10.1016/S0005-7967(01)00002-X

Fivush, R. (2011). The development of autobiographical memory. *Annu. Rev. Psychol.* 62, 559–582. doi:10.1146/annurev.psych.121208.131702

Foa, E. B., Gilboa-Schechtman, E., Amir, N., and Freshman, M. (2000). Memory bias in generalized social phobia: remembering negative emotional expressions. *J. Anxiety Disord.* 14, 501–519. doi:10.1016/S0887-6185(00)00036-0

Foa, E. B., and Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychol. Bull.* 99, 20–35. doi:10.1037/0033-2909.99.1.20

Foa, E. B., Molnar, C., and Cashman, L. (1995). Change in rape narratives during exposure therapy for posttraumatic stress disorder. *J. Trauma Stress* 8, 675–690. doi:10.1002/jts.2490080409

Gilboa, A. (2004). Autobiographical and episodic memory – one and the same? Evidence from prefrontal activation in neuroimaging studies. *Neuropsychologia* 42, 1336–1349. doi:10.1016/j.neuropsychologia.2004.02.014

Gladsjo, J. A., Rapaport, M. H., McKinney, R., Lucas, J. A., Rabin, A., Oliver, T., et al. (1998). A neuropsychological study of panic disorder: negative findings. *J. Affect. Disord.* 49, 123–131. doi:10.1016/S0165-0327(98)00006-8

Goddard, L., Dritschel, B., and Burton, A. (1996). Role of autobiographical memory in social problem solving and depression. *J. Abnorm. Psychol.* 105, 609–616. doi:10.1037/0021-843X.105.4.609

Golier, J. A., Yehuda, R., Lupien, S. J., and Harvey, P. D. (2003). Memory for trauma-related information in Holocaust survivors with PTSD. *Psychiatry Res.* 121, 133–143. doi:10.1016/S0925-4927(03)00120-3

Greisberg, S., and McKay, D. (2003). Neuropsychology of obsessive-compulsive disorder: a review and treatment implications. *Clin. Psychol. Rev.* 23, 95–117. doi:10.1016/S0272-7358(02)00232-5

Griffith, J. W., Sumner, J. A., Raes, F., Barnhofer, T., Debeer, E., and Hermans, D. (2012). Current psychometric and methodological issues in the measurement of overgeneral autobiographical memory. *J. Behav. Ther. Exp. Psychiatry.* 43(Suppl. 1), S21–S31. doi:10.1016/j.jbtep.2011.05.008

Hampton, R. R., and Schwartz, B. L. (2004). Episodic memory in nonhumans: what, and where, is when? *Curr. Opin. Neurobiol.* 14, 192–197. doi:10.1016/j.conb.2004.03.006

Harris, J. E. (1984). "Remembering to do things: a forgotten topic," in *Memory, Actions, and Absentmindedness*, eds J. E. Harris and P. E. Morris (New York: Academic Press), 71–92.

Harvey, A. G., Bryant, R. A., and Dang, S. T. (1998). Autobiographical memory in acute stress disorder. *J. Consult. Clin. Psychol.* 66, 500–506. doi:10.1037/0022-006X.66.3.500

Hayes, J. P., LaBar, K. S., McCarthy, G., Selgrade, E., Nasser, J., Dolcos, F., et al. (2011). Reduced hippocampal and amygdala activity predicts memory distortions for

trauma reminders in combat-related PTSD. *J. Psychiatr. Res.* 45, 660–669. doi:10.1016/j.jpsychires.2010.10.007

Heidenreich, T., Junghanns-Royack, K., and Stangier, U. (2007). Specificity of autobiographical memory in social phobia and major depression. *Br. J. Clin. Psychol.* 46, 19–33. doi:10.1348/014466506X106218

Heimberg, R. G. (2002). Cognitive–behavioral therapy for social anxiety disorder: current status and future directions. *Biol. Psychiatry* 51, 101–108. doi:10.1016/S0006-3223(01)01183-0

Hermans, D., Raes, F., Iberico, C., and Williams, J. M. G. (2006). Reduced autobiographical memory specificity, avoidance, and repression. *Behav. Brain Sci.* 29, 522–522. doi:10.1037/a0024535

Irish, M., Lawlor, B. A., Coen, R. F., and O'Mara, S. M. (2011). Everyday episodic memory in amnestic mild cognitive impairment: a preliminary investigation. *BMC Neurosci.* 12:80. doi:10.1186/1471-2202-12-80

Isaac, C. L., Cushway, D., and Jones, G. V. (2006). Is posttraumatic stress disorder associated with specific deficits in episodic memory? *Clin. Psychol. Rev.* 26, 939–955. doi:10.1016/j.cpr.2005.12.004

Kang, D. H., Kwon, J. S., Kim, J. J., Youn, T., Park, H. J., Kim, M. S., et al. (2003). Brain glucose metabolic changes associated with neuropsychological improvements after 4 months of treatment in patients with obsessive-compulsive disorder. *Acta Psychiatr. Scand.* 107, 291–297. doi:10.1034/j.1600-0447.2003.00070.x

Kangas, M., Henry, J. L., and Bryant, R. A. (2005). A prospective study of autobiographical memory and posttraumatic stress disorder following cancer. *J. Consult. Clin. Psychol.* 73, 293–299. doi:10.1037/0022-006X.73.2.293

Kinugawa, K., Schumm, S., Pollina, M., Depre, M., Jungbluth, C., Doulazmi, M., et al. (2013). Aging-related episodic memory decline: are emotions the key? *Front. Behav. Neurosci.* 7:2. doi:10.3389/fnbeh.2013.00002

Kleim, B., and Ehlers, A. (2008). Reduced autobiographical memory specificity predicts depression and posttraumatic stress disorder after recent trauma. *J. Consult. Clin. Psychol.* 76, 231–242. doi:10.1037/0022-006X.76.2.231

Krans, J., de Bree, J., and Bryant, R. A. (2013). Autobiographical memory bias in social anxiety. *Memory* 1–8. doi:10.1080/09658211.2013.844261

Kuelz, A. K., Hohagen, F., and Voderholzer, U. (2004). Neuropsychological performance in obsessive-compulsive disorder: a critical review. *Biol. Psychol.* 65, 185–236. doi:10.1016/j.biopsycho.2003.07.007

Lacerda, A. L. T., Dalgalarrondo, P., Caetano, D., Haas, G. L., Camargo, E. E., and Keshavan, M. S. (2003). Neuropsychological performance and regional cerebral blood flow in obsessive–compulsive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 27, 657–665. doi:10.1016/S0278-5846(03)00076-9

Lang, P. J. (1985). "The cognitive psychophysiology of emotion: fear and anxiety," in *Anxiety and the Anxiety Disorders*, eds A. H. Tuma and J. D. Maser (Hillsdale, NJ: Erlbaum), 131–170.

LeMoult, J., and Joormann, J. (2012). Attention and memory biases in social anxiety disorder: the role of comorbid depression. *Cognit. Ther. Res.* 36, 47–57. doi:10.1007/s10608-010-9322-2

Lucas, J. A., Telch, M. J., and Bigler, E. D. (1991). Memory functioning in panic disorder: a neuropsychological perspective. *J. Anxiety Disord.* 5, 1–20. doi:10.1016/0887-6185(91)90013-J

Lundh, L. G., Czyzykow, S., and Öst, L. G. (1997). Explicit and implicit memory bias in panic disorder with agoraphobia. *Behav. Res. Ther.* 35, 1003–1014. doi:10.1016/S0005-7967(97)00063-6

Lundh, L. G., and Öst, L. G. (1996). Recognition bias for critical faces in social phobics. *Behav. Res. Ther.* 34, 787–794. doi:10.1016/0005-7967(96)00035-6

Lundh, L. G., and Öst, L. G. (1997). Explicit and implicit memory bias in social phobia: the role of subdiagnostic type. *Behav. Res. Ther.* 35, 305–317. doi:10.1016/S0005-7967(96)00122-2

MacCallum, F., and Bryant, R. A. (2010). Impaired social problem solving in complicated grief. *Br. J. Clin. Psychol.* 49, 577–590. doi:10.1348/014466510X487040

MacLeod, C., and McLaughlin, K. (1995). Implicit and explicit memory bias in anxiety: a conceptual replication. *Behav. Res. Ther.* 33, 1–14. doi:10.1016/0005-7967(94)E0004-3

Maddock, R. J. (1999). The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci.* 22, 310–316. doi:10.1016/S0166-2236(98)01374-5

Maddock, R. J., Buonocore, M. H., Kile, S. J., and Garrett, A. S. (2003). Brain regions showing increased activation by threat-related words in panic disorder. *Neuroreport* 14, 325–328. doi:10.1097/00001756-200303030-00006

Margraf, J. (2000). *Lehrbuch der Verhaltenstherapie*. Berlin: Springer.

Margraf, J., and Ehlers, A. (1989). "Etiological models of panic – psychophysiological and cognitive aspects," in *Panic Disorder: Research and Therapy*, ed. R. Baker (Chichester: Wiley), 205–231.

Margraf, J., Ehlers, A., and Roth, W. T. (1986a). Biological models of panic disorder and agoraphobia – a review. *Behav. Res. Ther.* 24, 553–567. doi:10.1016/0005-7967(86)90036-7

Margraf, J., Ehlers, A., and Roth, W. T. (1986b). Sodium lactate infusions and panic attacks: a review and critique. *Psychosom. Med.* 48, 23–51.

Mataix-Cols, D., Alonso, P., Pifarre, J., Menchon, J. L., and Vallejo, J. (2002). Neuropsychological performance in medicated vs. unmedicated patients with obsessive–compulsive disorder. *Psychiatry Res.* 109, 255–264. doi:10.1016/S0165-1781(02)00024-0

Mathews, A., and MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol.* 1, 167–195. doi:10.1146/annurev.clinpsy.1.102803.143916

McDermott, K. B., Szpunar, K. K., and Christ, S. E. (2009). Laboratory-based and autobiographical retrieval tasks differ substantially in their neural substrates. *Neuropsychologia* 47, 2290–2298. doi:10.1016/j.neuropsychologia.2008.12.025

McNally, R. J. (1990). Psychological approaches to panic disorder: a review. *Psychol. Bull.* 108, 403–419. doi:10.1037/0033-2909.108.3.403

McNally, R. J. (1997). Memory and anxiety disorders. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 352, 1755–1759. doi:10.1098/rstb.1997.0158

McNally, R. J., Foa, E. B., and Donnell, C. D. (1989). Memory bias for anxiety information in patients with panic disorder. *Cogn. Emot.* 3, 27–44. doi:10.1080/02699938908415234

McNally, R. J., Lasko, N. B., Macklin, M. L., and Pitman, R. K. (1995). Autobiographical memory disturbance in combat-related posttraumatic stress disorder. *Behav. Res. Ther.* 33, 619–630. doi:10.1016/0005-7967(95)00007-K

McNally, R. J., Litz, B. T., Prassas, A., Shin, L. M., and Weathers, F. W. (1994). Emotional priming of autobiographical memory in posttraumatic stress disorder. *Cogn. Emot.* 8, 351–367. doi:10.1371/journal.pone.0058150

Mitte, K. (2008). Memory bias for threatening information in anxiety and anxiety disorders: a meta-analytic review. *Psychol. Bull.* 134, 886–911. doi:10.1037/a0013343

Mogg, K., Mathews, A., and Weinman, J. (1987). Memory bias in clinical anxiety. *J. Abnorm. Psychol.* 96, 94–98. doi:10.1037/0021-843X.96.2.94

Moore, S. A., and Zoellner, L. A. (2007). Overgeneral autobiographical memory and traumatic events: an evaluative review. *Psychol. Bull.* 133, 419–437. doi:10.1037/0033-2909.133.3.419

Moradi, A. R., Abdi, A., Fathi-Ashtiani, A., Dalgleish, T., and Jobson, L. (2012). Overgeneral autobiographical memory recollection in Iranian combat veterans with posttraumatic stress disorder. *Behav. Res. Ther.* 50, 435–441. doi:10.1016/j.brat.2012.03.009

Morgan, J. (2010). Autobiographical memory biases in social anxiety. *Clin. Psychol. Rev.* 30, 288–297. doi:10.1016/j.cpr.2009.12.003

Moscovitch, D. A., Gavric, D. L., Merrifield, C., Bielak, T., and Moscovitch, M. (2011). Retrieval properties of negative vs. positive mental images and autobiographical memories in social anxiety: outcomes with a new measure. *Behav. Res. Ther.* 49, 505–517. doi:10.1016/j.brat.2011.05.009

Mur, M., Portella, M. J., Martinez-Aran, A., Pifarre, J., and Vieta, E. (2009). Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. *Psychopathology* 42, 148–156. doi:10.1159/000207456

Neshat-Doost, H. T., Dalgleish, T., Yule, W., Kalantari, M., Ahmadi, S. J., Dyregov, A., et al. (2013). Enhancing autobiographical memory specificity through cognitive training: an intervention for depression translated from basic science. *Clin. Psychol. Sci.* 1, 84–92. doi:10.1177/2167702612454613

Neylan, T. C., Lenoci, M., Rothlind, J., Metzler, T. J., Schuff, N., Du, A., et al. (2004). Attention, learning, and memory in posttraumatic stress disorder. *J. Trauma Stress* 17, 41–46. doi:10.1023/B:JOTS.0000014675.75686.ee

Nezu, A. M., Nezu, C. M., and Lombardo, E. (2003). "Problem-solving therapy," in *Cognitive Behavior Therapy: Applying Empirically Supported Techniques in your Practice*, eds W. O'Donohue, J. E. Fisher, and S. C. Hayes (Hoboken: John Wiley & Sons), 301–307.

Nunn, J., Stevenson, R., and Whalan, G. (1984). Selective memory effects in agoraphobic patients. *Br. J. Clin. Psychol.* 23, 195–201. doi:10.1111/j.2044-8260.1984.tb00646.x

Olley, A., Malhi, G., and Sachdev, P. (2007). Memory and executive functioning in obsessive-compulsive disorder: a selective review. *J. Affect. Disord.* 104, 15–23. doi:10.1016/j.jad.2007.02.023

Öst, L. G., and Hugdahl, K. (1981). Acquisition of phobias and anxiety response patterns in clinical patients. *Behav. Res. Ther.* 19, 439–447. doi:10.1016/0005-7967(81)90134-0

Pauli, P., Dengler, W., and Wiedemann, G. (2005). Implicit and explicit memory processes in panic patients as reflected in behavioral and electrophysiological measures. *J. Behav. Ther. Exp. Psychiatry* 36, 111–127. doi:10.1016/j.jbtep.2004.08.003

Paunovi, N., Lundh, L. G., and Öst, L. G. (2002). Attentional and memory bias for emotional information in crime victims with acute posttraumatic stress disorder (PTSD). *J. Anxiety Disord.* 16, 675–692. doi:10.1016/S0887-6185(02)00136-6

Pause, B. M., Jungbluth, C., Adolph, D., Pietrowsky, R., and Dere, E. (2010). Induction and measurement of episodic memories in healthy adults. *J. Neurosci. Methods* 189, 88–96. doi:10.1016/j.jneumeth.2010.03.016

Pause, B. M., Zlomuzica, A., Kinugawa, K., Mariani, J., Pietrowsky, R., and Dere, E. (2013). Perspectives on episodic-like and episodic memory. *Front. Behav. Neurosci.* 7:33. doi:10.3389/fnbeh.2013.00033

Penadés, R., Catalán, R., Andrés, S., Salamero, M., and Gastó, C. (2005). Executive function and nonverbal memory in obsessive-compulsive disorder. *Psychiatry Res.* 133, 81–90. doi:10.1016/j.psychres.2004.09.005

Pérez-López, J. R., and Woody, S. R. (2001). Memory for facial expressions in social phobia. *Behav. Res. Ther.* 39, 967–975. doi:10.1016/S0005-7967(00)00103-0

Pickles, A. J., and van den Broek, M. D. (1988). Failure to replicate evidence for phobic schemata in agoraphobic patients. *Br. J. Clin. Psychol.* 27, 271–272. doi:10.1111/j.2044-8260.1988.tb00788.x

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memory over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329. doi:10.1016/j.neuropsychologia.2009.01.020

Pishyar, R., Harris, L. M., and Menzies, R. G. (2004). Attentional bias for words and faces in social anxiety. *Anxiety Stress Coping* 17, 23–36. doi:10.1080/10615800310001601458

Plancher, G., Gyselinck, V., Nicolas, S., and Piolino, P. (2010). Age effect on components of episodic memory and feature binding: a virtual reality study. *Neuropsychology* 24, 379–390. doi:10.1037/a0018680

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., and Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia* 50, 592–602. doi:10.1016/j.neuropsychologia.2011.12.013

Pollock, L. R., and Williams, J. M. (2001). Effective problem solving in suicide attempters depends on specific autobiographical recall. *Suicide Life Threat Behav.* 31, 386–396. doi:10.1521/suli.31.4.386.22041

Purcell, R., Maruff, P., Kyrios, M., and Pantelis, C. (1998). Neuropsychological deficits in obsessive–compulsive disorder. A comparison with unipolar depression, panic disorder and, normal controls. *Arch. Gen. Psychiatry* 55, 415–423. doi:10.1001/archpsyc.55.5.415

Radomsky, A. S., and Rachman, S. (1999). Memory bias in obsessive–compulsive disorder (OCD). *Behav. Res. Ther.* 37, 605–618. doi:10.1016/S0005-7967(98)00151-X

Raes, F., Williams, J. M. G., and Hermans, D. (2009). Reducing cognitive vulnerability to depression: a preliminary investigation of Memory Specificity Training (MEST) in patients with depressive symptomatology. *J. Behav. Ther. Exp. Psychiatry* 40, 24–38. doi:10.1016/j.jbtep.2008.03.001

Rapee, R. M., and Heimberg, R. G. (1997). A cognitive–behavioral model of anxiety in social phobia. *Behav. Res. Ther.* 35, 741–756. doi:10.1016/S0005-7967(97)00022-3

Rapee, R. M., McCallum, S. L., Melville, L. F., Ravenscroft, H., and Rodney, J. M. (1994). Memory bias in social phobia. *Behav. Res. Ther.* 32, 89–99. doi:10.1016/0005-7967(94)90087-6

Rawal, A., and Rice, F. (2012). Examining overgeneral autobiographical memory as a risk factor for adolescent depression. *J. Am. Acad. Child Psychol.* 51, 518–527. doi:10.1016/j.jaac.2012.02.025

Rinck, M., and Becker, E. S. (2005). A comparison of attentional biases and memory biases in women with social phobia and major depression. *J. Abnorm. Psychol.* 114, 62–74. doi:10.1037/0021-843X.114.1.62

Robjant, K., and Fazel, M. (2010). The emerging evidence for narrative exposure therapy: a review. *Clin. Psychol. Rev.* 30, 1030–1039. doi:10.1016/j.cpr.2010.07.004

Rusted, J., and Dighton, K. (1991). Selective processing of threat-related material by spider phobics in a prose recall task. *Cogn. Emot.* 5, 123–132. doi:10.1080/02699939108411029

Sachs, G., Anderer, P., Margreiter, N., Semlitsch, H., Saletu, B., and Katschnig, H. (2004). P300 event-related potentials and cognitive function in social phobia. *Psychiatry Res.* 131, 249–261. doi:10.1016/j.pscychresns.2004.05.005

Savage, C. R., Baer, L., Keuthen, N. J., Brown, H. D., Rauch, S. L., and Jenike, M. A. (1999). Organizational strategies mediate non-verbal memory impairment in obsessive–compulsive disorder. *Biol. Psychiatry* 45, 905–916. doi:10.1016/S0006-3223(98)00278-9

Savage, C. R., Deckersbach, T., Wilhelm, S., Rauch, S. L., Baer, L., Reid, T., et al. (2000). Strategic processing and episodic memory impairment in obsessive compulsive disorder. *Neuropsychology* 14, 141–151. doi:10.1037/0894-4105.14.1.141

Schacter, D. L., Norman, K. A., and Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annu. Rev. Psychol.* 49, 289–318. doi:10.1146/annurev.psych.49.1.289

Serrano, J. P., Latorre, J. M., Gatz, M., and Montanes, J. (2004). Life review therapy using autobiographical retrieval practice for older adults with depressive symptomatology. *Psychol. Aging* 19, 270–277. doi:10.1037/0882-7974.19.2.272

Shin, L. M., Shin, P. S., Heckers, S., Krangel, T. S., Macklin, M. L., Orr, S. P., et al. (2004). Hippocampal function in posttraumatic stress disorder. *Hippocampus* 14, 292–300. doi:10.1002/hipo.10183

Soravia, L. M., Heinrichs, M., Aerni, A., Maroni, C., Schelling, G., Ehlert, U., et al. (2006). Glucocorticoids reduce phobic fear in humans. *Proc. Natl. Acad. Sci. U.S.A.* 103, 5585–5590. doi:10.1073/pnas.0509184103

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol. Learn. Mem.* 82, 171–177. doi:10.1016/j.nlm.2004.06.005

Staugaard, S. R. (2010). Threatening faces and social anxiety: a literature review. *Clin. Psychol. Rev.* 30, 669–690. doi:10.1016/j.cpr.2010.05.001

Stein, M. B., Kennedy, C. M., and Twamley, E. W. (2002). Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol. Psychiatry* 52, 1079–1088. doi:10.1016/S0006-3223(02)01414-2

Suddendorf, T., and Corballis, M. C. (2007). The evolution of foresight: what is mental time travel, and is it unique to humans? *Behav. Brain Sci.* 30, 299–313. doi:10.1017/S0140525X07001975

Sumner, J. A., Griffith, J. W., and Mineka, S. (2010). Overgeneral autobiographical memory as a predictor of the course of depression: a meta-analysis. *Behav. Res. Ther.* 48, 614–625. doi:10.1016/j.brat.2010.03.013

Sutherland, K., and Bryant, R. A. (2007). Autobiographical memory in posttraumatic stress disorder before and after treatment. *Behav. Res. Ther.* 45, 2915–2923. doi:10.1016/j.brat.2007.08.009

Sutherland, K., and Bryant, R. A. (2008a). Social problem solving and autobiographical memory in post traumatic stress disorder. *Behav. Res. Ther.* 46, 154–161. doi:10.1016/j.brat.2007.10.005

Sutherland, K., and Bryant, R. A. (2008b). Autobiographical memory and the self-memory system in posttraumatic stress disorder. *J. Anxiety Disord.* 22, 555–560. doi:10.1016/j.janxdis.2007.03.008

Sutterby, S. R., and Bedwell, J. S. (2012). Lack of neuropsychological deficits in generalized social phobia. *PLoS ONE* 7:e42675. doi:10.1371/journal.pone.0042675

Szpunar, K. K., Watson, J. M., and McDermott, K. B. (2007). Neural substrates of envisioning the future. *Proc. Natl. Acad. Sci. U.S.A.* 104, 642–647. doi:10.1073/pnas.0610082104

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., et al. (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *J. Affect. Disord.* 109, 286–299. doi:10.1016/j.jad.2007.12.234

Tallis, F., Pratt, P., and Jamani, N. (1999). Obsessive compulsive disorder, checking, and non-verbal memory: a neuropsychological investigation. *Behav. Res. Ther.* 37, 161–166. doi:10.1016/S0005-7967(98)00075-8

Thomaes, K., Dorrepaal, E., Draijer, N. P., de Ruiter, M. B., Elzinga, B. M., van Balkom, A. J., et al. (2009). Increased activation of the left hippocampus region

in Complex PTSD during encoding and recognition of emotional words: a pilot study. *Psychiatry Res.* 171, 44–53. doi:10.1016/j.pscychresns.2008.03.003

Thorpe, S. J., and Salkovskis, P. M. (2000). Recall and recognition memory for spider information. *J. Anxiety Disord.* 14, 359–375. doi:10.1016/S0887-6185(00)00028-1

Tolin, D. F., Abramowitz, J. S., Brigidi, B. D., Amir, N., Street, G. P., and Foa, E. B. (2001). Memory and memory confidence in obsessive-compulsive disorder. *Behav. Res. Ther.* 39, 913–927. doi:10.1016/S0005-7967(00)00064-4

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–403.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Tuna, S., Tekcan, A. I., and Topçuoglu, V. (2005). Memory and metamemory in obsessive-compulsive disorder. *Behav. Res. Ther.* 43, 15–27. doi:10.1016/j.brat.2003.11.001

Van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Cath, D. C., van Balkom, A. J., van Hartskamp, J., et al. (2005). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 62, 301–309. doi:10.1001/archpsyc.62.3.301

van Tol, M. J., Demenescu, L. R., van der Wee, N. J., Kortekaas, R., Marjan, M. N., Boer, J. A., et al. (2012). Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. *Biol. Psychiatry* 71, 593–602. doi:10.1016/j.biopsych.2011.11.016

Van Vreeswijk, M. F., and de Wilde, E. (2004). Autobiographical memory specificity, psychopathology, depressed mood, and the use of the autobiographical memory test: a meta analysis. *Behav. Res. Ther.* 42, 731–743. doi:10.1016/S0005-7967(03)00194-3

Vandermorris, S., Sheldon, S., Winocur, G., and Moscovitch, M. (2013). Differential contributions of executive and episodic memory functions to problem solving in younger and older adults. *J. Int. Neuropsychol. Soc.* 18, 1–10. doi:10.1017/S1355617713000982

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N. Jr., and Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam Veterans: PTSD and no disorder comparisons. *Neuropsychology* 16, 5–14. doi:10.1037/0894-4105.16.1.5

Vrana, S. R., Roodman, A., and Beckham, J. C. (1995). Selective processing of trauma-relevant words in posttraumatic stress disorder. *J. Anxiety Disord.* 9, 515–530. doi:10.1016/0887-6185(95)00028-M

Walker, M. P., Brakefield, T., Hobson, J. A., and Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425, 616–620. doi:10.1038/nature01930

Watkins, E. R. (2008). Constructive and unconstructive repetitive thoughts. *Psychol. Bull.* 134, 163–206. doi:10.1037/0033-2909.134.2.163

Watts, F. N., and Coyle, K. (1992). Recall bias for stimulus and response anxiety words in spider phobics. *Anxiety Res.* 4, 315–323. doi:10.1080/08917779208248799

Watts, F. N., and Dalgleish, T. (1991). Memory for phobia-related words in spider phobics. *Cogn. Emot.* 5, 313–329. doi:10.1080/02699939108411043

Wenzel, A., and Cochran, C. K. (2006). Autobiographical memories prompted by automatic thoughts in panic disorder and social phobia. *Cogn. Behav. Ther.* 35, 129–137. doi:10.1080/16506070600583130

Wenzel, A., Finstrom, N., Jordan, J., and Brendle, J. R. (2005). Memory and interpretation of visual representations of threat in socially anxious and nonanxious individuals. *Behav. Res. Ther.* 43, 1029–1044. doi:10.1016/j.brat.2004.07.004

Wenzel, A., and Holt, C. S. (2002). Memory bias against threat in social phobia. *Br. J. Clin. Psychol.* 41, 73–79. doi:10.1348/014466502163804

Wenzel, A., Jackson, L. C., Brendle, J. R., and Pinna, K. (2003). Autobiographical memories associated with feared stimuli in fearful and nonfearful individuals. *Anxiety Stress Coping* 16, 1–15. doi:10.1080/1061580021000009656

Wenzel, A., Jackson, L. C., and Holt, C. S. (2002). Social phobia and the recall of autobiographical memories. *Depress. Anxiety* 15, 186–189. doi:10.1002/da.10053

Wenzel, M. M., Werner, C. K., Cochran, C. S., and Holt, A. (2004). Differential pattern of autobiographical memory retrieval in social phobic and nonanxious individuals. *Behav. Cogn. Psychother.* 32, 1–13.

Wessel, I., Meeren, M., Peeters, F., Arntz, A., and Merckelbach, H. (2001). Correlates of autobiographical memory specificity: the role of depression, anxiety and childhood trauma. *Behav. Res. Ther.* 39, 409–421. doi:10.1016/S0005-7967(00)00011-5

Whalley, M. G., Rugg, M. D., Smith, A. P., Dolan, R. J., and Brewin, C. R. (2009). Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. *Brain Cogn.* 69, 98–107. doi:10.1016/j.bandc.2008.05.008

Wilhelm, S., McNally, R. J., Baer, L., and Florin, I. (1996). Directed forgetting in obsessive–compulsive disorder. *Behav. Res. Ther.* 34, 633–641. doi:10.1016/0005-7967(96)00040-X

Wilhelm, S., McNally, R. J., Baer, L., and Florin, I. (1997). Autobiographical memory in obsessive-compulsive disorder. *Br. J. Clin. Psychol.* 36, 21–31. doi:10.1111/j.2044-8260.1997.tb01227.x

Williams, J. M. G. (2006). Capture and rumination, functional avoidance, and executive control (CaRFAX): three processes that underlie overgeneral memory. *Cogn. Emot.* 20, 548–568. doi:10.1016/j.cpr.2011.10.003

Williams, J. M. G., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., et al. (2007). Autobiographical memory specificity and emotional disorder. *Psychol. Bull.* 133, 122–148. doi:10.1037/0033-2909.133.1.122

Williams, J. M. G., and Broadbent, K. (1986). Autobiographical memory in suicide attempters. *J. Abnorm. Psychol.* 95, 144–149. doi:10.1037/0021-843X.95.2.144

Williams, J. M. G., Ellis, N. C., Tyers, C., Healy, H., Rose, G., and MacLeod, A. K. (1996). The specificity of autobiographical memory and imageability of the future. *Mem. Cognit.* 24, 116–125. doi:10.3758/BF03197278

Williams, J. M. G., Teasdale, J. D., Segal, Z. V., and Soulsby, J. (2000). Mindfulness-based cognitive therapy reduces overgeneral autobiographical memory in formerly depressed patients. *J. Abnorm. Psychol.* 109, 150–155. doi:10.1037/0021-843X.109.1.150

Zeitlin, S. B., and McNally, R. J. (1991). Implicit and explicit memory bias for threat in post-traumatic stress disorder. *Behav. Res. Ther.* 29, 451–457. doi:10.1016/0005-7967(91)90129-Q

Zucker, D., Taylor, C. B., Brouillard, M., Ehlers, A., Margraf, J., Roth, W. T., et al. (1989). Cognitive aspects of panic attacks: content, course, and relationship to laboratory stressors. *Br. J. Psychiatry* 155, 86–91. doi:10.1192/bjp.155.1.86

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Directed forgetting in post-traumatic-stress-disorder: a study of refugee immigrants in Germany

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People with post-traumatic stress disorder (PTSD) often suffer from memory disturbances. In particular, previous studies suggest that PTSD patients perform atypically on tests of directed forgetting, which may be mediated by an altered emotional appraisal of the presented material. Also, a special role of dissociative symptoms in traumatized individuals' memory performance has been suggested. Here, we investigate these issues in traumatized immigrants in Germany. In an item-method directed forgetting task, pictures were presented individually, each followed by an instruction to either remember or forget it. Later, recognition memory was tested for all pictures, regardless of initial instruction. Overall, the PTSD group's discrimination accuracy was lower than the control group's, as PTSD participants produced fewer hits and more false alarms, but the groups did not differ in directed forgetting itself. Moreover, the more negatively participants evaluated the stimuli, the less they were able to discriminate old from new items. Participants with higher dissociation scores were particularly poor at recognizing to-be-forgotten items. Results confirm PTSD patients' general discrimination deficits, but provide no evidence for a distinct directed forgetting pattern in PTSD. Furthermore, data indicate that, in general, more negatively perceived items are discriminated with less accuracy than more positively appraised ones. Results are discussed in the larger context of emotion and stress-related modulations of episodic memory, with particular focus on the role of dissociative symptoms.

Keywords: directed forgetting, post-traumatic stress disorder, emotion, dissociation

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a possible aftereffect of extremely traumatic life experiences, that is, events which threaten one's own or others' lives or physical integrity and to which the individual reacts with intense feelings of fear or helplessness (APA, 1994). The disorder is characterized by symptoms of re-experiencing, avoidance/emotional numbing, and heightened arousal, persisting for a month at minimum.

Memory disturbances are a core feature of PTSD (for a review, see McNally, 2006). They can alternate between recurrent, intrusive recollections, and an inability to recall autobiographical information, including the traumatic experience, a paradox reflected in the diagnostic criteria (APA, 1994). On laboratory tasks, memory deficits in PTSD become apparent as a reduced ability to recall recently studied items in explicit tests and as an increased tendency to produce false memories in free recall (see Brewin et al., 2007) and old–new recognition tests (Bremner et al., 2000; Zoellner et al., 2000; Goodman et al., 2011).

The directed forgetting paradigm (DF; for an overview, see Johnson, 1994) is well-suited to explore cognitive abnormalities in PTSD. It can be used to test for the capability to selectively remember relevant and to forget irrelevant information and to distinguish presented items from similar, but never presented material. In DF tasks, participants are shown items and instructed to remember some of them but forget others. Later, memory is tested for both remember (R) and forget (F) items. Usually, participants are able to reproduce more R- than F-items – the DF effect. Conversely, false memories are typically higher in the F than in the R condition (e.g., Kimball and Bjork, 2002; Zwissler et al., 2011, 2012). In item-method DF, where each single item is followed by an instruction to either remember or forget it, the DF effect is generally attributed to selective encoding, since participants can stop encoding items immediately after receiving F instructions and can selectively rehearse after R instructions. In item-method DF, effects are seen on both free recall and recognition tasks.

Several studies have addressed modulations of item-method DF in clinical populations (for a review, see Geraerts and McNally, 2008). In particular, the hypothesis has been examined that traumatized individuals [particularly survivors of childhood sexual abuse (CSA)] use an avoidant or dissociative encoding style and are therefore better able to disengage from threatening events resulting in particularly poor encoding of emotionally negative F-items and larger DF effects (Terr, 1994). However, subsequent studies with traumatized participants in general or PTSD patients were inconsistent (see Geraerts and McNally, 2008).

For instance, Cloitre et al. (1996) found a larger recall advantage for R- versus F-items in individuals with borderline personality disorder and parental abuse histories, relative to borderline personality disorder without abuse histories or healthy controls. However, in a subsequent study, participants with borderline personality disorder, unlike controls, exhibited superior recall for negative F words, providing no evidence for participants' avoidant encoding of threatening information (Korfine and Hooley, 2000).

McNally and his colleagues investigated in several DF studies whether individuals with repressed, recovered, or continuous memories of CSA performed differently from participants without a history of CSA (e.g., McNally et al., 1998, 2001, 2004). Under the avoidant encoding hypothesis, CSA survivors, particularly those who claimed to have forgotten their abuse (i.e., participants with repressed or recovered memories), should forget more trauma-related words than participants with continuous memories or those without a history of CSA. Yet overall, participants reporting repressed or recovered memories of CSA did not differ from the other groups in DF performance, providing no evidence for avoidant encoding.

Zoellner et al. (2003) investigated DF in PTSD patients and healthy controls under the assumption that the current mood state affects DF patterns. They induced either a dissociative or a serene mood in PTSD patients and controls before the DF task. Although a standard DF effect occurred in the serenity condition, contrary to predictions this effect was completely absent in the dissociation condition, suggesting that, if anything, the dissociative state reduced rather than increased directed forgetting. Moreover, the PTSD and control groups recalled comparable numbers of threat-related items (a finding similar to McNally et al., 1998). Thus, the study neither provided evidence for avoidant nor for intrusive encoding of threatening information in PTSD. DePrince and Freyd (2001, 2004) argued that dissociation may facilitate DF performance under divided attention, in particular. Indeed, in a pre-selected student population, high-dissociative students recalled fewer trauma-related and more neutral items under divided attention conditions than did low-dissociative students. However, replications by other authors failed (McNally et al., 2005; Devilly et al., 2007; but see DePrince et al., 2007; Devilly and Ciorciari, 2007 for critical discussions).

Some evidence that traumatized individuals may indeed be better at forgetting particularly threatening material and that dissociative symptoms may play a special role comes from studies on participants with acute stress disorder (ASD; Moulds and Bryant, 2002, 2005): ASD patients recalled fewer trauma-related F words compared to controls and trauma-exposed participants without ASD. The authors suspected a modulatory role of dissociative symptoms, which are essential for the diagnosis of ASD but not PTSD. According to Moulds and Bryant, these might have caused superior forgetting in the ASD group.

So far, the evidence on DF patterns in traumatized individuals is very heterogeneous. Regarding the impact of emotional stimuli, one theory posits that traumatized individuals are superior at forgetting in general and at forgetting emotional or threatening information in particular. However, some of the above cited studies point to reduced DF, especially for emotional material. Similarly, Zwissler et al. (2012) found, in an item-method DF study on Ugandan civil war victims with and without PTSD, a DF effect in the control but not in the PTSD group. Furthermore, PTSD participants produced more false alarms than controls and rated the stimuli as significantly more arousing than Non-PTSD participants. Higher arousal ratings were associated with a reduced DF effect, suggesting that the attenuation of DF in PTSD was mediated by increased subjective arousal, in line with the finding that healthy participants in general have reduced DF for emotional information on recognition tasks (Hauswald et al., 2011; Zwissler et al., 2011).

Still, a role for a dissociative processing style resulting in more DF has been identified by some studies (Terr, 1994; DePrince and Freyd, 2001, 2004; Moulds and Bryant, 2002, 2005). Moreover, recently hyper-aroused and dissociative PTSD sub-types have been suggested. These sub-types are supposed to differ in their physiologic and psychological response patterns to trauma reminders, the dissociative sub-type being characterized by emotional numbing, in particular (Schauer and Elbert, 2010). If so, different admixtures of these sub-types in different memory experiments may have contributed to the inconsistent results in PTSD.

Overall, emotional content of the stimuli (e.g., valence and arousal), the trauma relevance of the stimuli, as well as the patients' dissociative symptoms have been suggested to affect DF in PTSD, but so far no study has considered these factors simultaneously. The present study investigates the DF performance of asylum seekers with and without PTSD in Germany, specifically examining dissociative symptoms and subjective stimulus appraisal as possible mediating factors. Because of their frequent exposure to traumatic events during war and political persecution, PTSD prevalence rates of up to 40% have been reported for asylum seekers (Gäbel et al., 2006; see also Lindert et al., 2008). However, the cognitive consequences of this fact are largely unexplored. We addressed DF patterns in this population in a language-free pictorial task, followed by arousal and valence ratings of the stimuli. Group differences in overall recognition memory (hits, false alarms, discrimination accuracy, response bias) and directed forgetting were investigated and the relationship between DF, participants' dissociation scores and stimulus appraisals were examined.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-five migrants and refugees took part in the study, 12 being diagnosed with PTSD and 13 serving as controls.

For the PTSD group, individuals currently investigated or treated at the University of Konstanz Outpatient Clinic for Refugees (*Psychologische Forschungs- und Modellambulanz für Flüchtlinge*) were invited to participate. They all met DSM-IV criteria for PTSD (APA, 1994), as previously assessed with the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) in the course of standard diagnostic procedures at the outpatient department. The PTSD group consisted of eight women and four men. Five participants were from African countries, three from Turkey, two from Kosovo, and one each from Iran and Iraq. On average, they were 32.3 years old (SD = 9.28) and had received 7.67 years of education (SD = 5.50).

The control group was partly recruited at the outpatient clinic (controls or interpreters of previous studies; $n = 6$) and partly

through information and language courses for migrants ($n = 7$). All were screened for PTSD using the Post-traumatic Diagnostic Scale (PDS; Foa et al., 1997), and none of them met DSM-IV criteria (APA, 1994). Efforts were made to match the control group to the PTSD group: the controls had migrated from countries similar to the PTSD group's (five were from African countries, two from Iran, and one from Iraq, Turkey, Russia, Belarus, Romania, and Hungary, respectively) and neither differed significantly from the PTSD group in age [$M = 34.5$, SD $= 11.2$; $t(23) = 0.53$, $p = 0.60$[1]] nor in gender distribution [10 women versus three men; $L\chi^2$ $(1) = 0.33$, $p = 0.67$]. However, they had received formal education approximately 7 years longer than had the PTSD group [$M = 14.9$, SD $= 3.19$; $t(17) = 3.97$, $p = 0.001$].

STIMULI, DESIGN, AND PROCEDURES

After giving informed consent, participants were administered the Dissociative Experiences Scale (DES; Bernstein and Putnam, 1986). The DES is a self-assessment questionnaire measuring dissociative phenomena like amnesia, absorption, and alienation. Its 28 items describe experiences such as, "Some people have the experience of finding new things among their belongings that they do not remember buying" and, "Some people have the experience of feeling that other people, objects, and the world around them are not real." For each experience, participants rate the frequency of occurrence on a scale from 0 to 100, and the mean of these item scores constitutes the DES score. The DES possesses good reliability and validity (e.g., Frischholz et al., 1990; Dubester and Braun, 1995). For participants who neither spoke German nor English fluently, interpreters translated during the whole session.

Completion of the DES was followed by the DF task. Here, two sets of 28 complex photographs served as stimuli. The pictures showed scenes of daily life, such as landscapes, vehicles, or people (see **Figure 1** for examples). The sets were paired such that every picture in one set had a similar counterpart in the other set. In the learning phase, the 28 pictures of one set were presented on a computer screen in random order for 4000 ms each. Every picture was followed by a 2000 ms instruction indicating whether participants should memorize the picture (instruction "MMM" for the German word "merken") or forget it ("VVV" for "vergessen"). Then, a fixation cross appeared for 2000 ms before the next photograph was presented. After the learning phase, participants worked on "Tangram" puzzles for 5 min as a distracter task. In the ensuing recognition phase, the 28 pictures of the learning set were presented randomly intermixed with the 28 photographs of the second set, which served as lures. Each picture was shown for 1000 ms and participants made old–new decisions by pressing the right (for *old*) or left (for *new*) mouse button within a time limit of 4000 ms. Participants were informed that new pictures could look quite similar to old ones, and, importantly, that their old–new decisions should be independent of the original instructions associated with the pictures (i.e., participants were supposed to chose *old* if they recognized pictures regardless of whether they had been designated as R or F).

[1]Before comparing means, equality of variances was examined using Levene's test. For unequal variances, corrected t-values and degrees of freedom are presented.



FIGURE 1 | Three exemplary pairs of used target and distracter pictures illustrating the range of emotional intensity and valence covered by the stimuli as well as target – distracter similarity.

Afterward, participants rated each of the 56 photographs on the dimensions valence, arousal, and trauma relevance: they indicated on nine-point scales whether they found a picture pleasant or unpleasant (valence), arousing or quiet (arousal), and whether it reminded them of their own traumatic experiences (trauma relevance). Controls were additionally screened for PTSD with the PDS at the end of the session before they – like PTSD participants – received a compensation of 20 €.

STATISTICAL ANALYSIS

Statistical calculations were carried out with SPSS Version 17.0. In a first step, recognition data were statistically analyzed by means of mixed-model ANOVAs with response type and instruction as within factors (hits R, hits F, false alarms R, false alarms F) and group as between factor (PTSD versus control). Effects are reported as significant at $p < 0.05$. In a second step, group differences in picture appraisals and dissociative symptoms were assessed and their correlative relationship explored. Finally, the influence of picture appraisals and dissociative symptoms on memory performance was addressed by entering mean valence, arousal, and trauma relevance ratings as well as DES scores individually into the ANOVA model as covariates. Furthermore, targeted analyses investigated the linear relationships between recognition accuracy for F and R items and valence, arousal, trauma relevance as well as dissociative symptoms.

RESULTS

RECOGNITION MEMORY AND DIRECTED FORGETTING

Table 1 presents mean hit and false alarm rates in the R and F conditions for the sample as a whole as well as for the two subgroups. Participants were included in the analyses if the number of pictures they designated as old was within one standard deviation around the mean of pictures designated as old across participants ($M = 28.9$, SD $= 7.31$; resulting in $n = 20$[2]). For hits,

[2]For the five excluded participants (four PTSD patients and one control), it has to be assumed that instructions were not understood. For example, one participant designated 53 of the 56 pictures in the recognition test as old (when in fact 28 were old); including these extreme "overestimators" would have inflated false alarm rates. Another participant, on the contrary, designated only 13 pictures as old; here, the

Table 1 | Mean hit and false alarm rates in the R and F conditions for the whole sample as well as separately for the PTSD and control group.

	Hits R (SD)	Hits F (SD)	False alarms R (SD)	False alarms F (SD)
Overall ($n = 20$)	0.77 (0.17)	0.77 (0.18)	0.23 (0.17)	0.30 (0.17)
PTSD ($n = 8$)	0.70 (0.19)	0.65 (0.20)	0.30 (0.20)	0.39 (0.14)
Control ($n = 12$)	0.82 (0.15)	0.85 (0.12)	0.18 (0.13)	0.24 (0.17)

a significant main effect of group [$F(1, 18) = 6.14, p = 0.023$] indicated that the control group produced more hits than the PTSD group. Regarding false alarms, there was a significant main effect of instruction [$F(1, 18) = 7.05$, $p = 0.016$], that is, participants produced more false alarms for F than R items and an effect of group [$F(1, 18) = 4.23$, $p = 0.054$], indicating that PTSD participants produced more false alarms than controls.

Next, hits and false alarms were considered contemporaneously, differentiating between discrimination accuracy (Pr = hits – false alarms) and response bias [Br = false alarms/(1–Pr)]. In terms of discrimination accuracy, a trend-level effect for instruction was observed [$F(1, 18) = 3.99$, $p = 0.061$; see **Figure 2**]: participants tended to show better discrimination accuracy for R than for F-items, that is, a DF effect. Moreover, the control group's discrimination accuracy was higher than PTSD group's, as demonstrated by a main effect of group [$F(1, 18) = 6.27, p = 0.022$]. There was no significant interaction of instruction and group [$F(1, 18) = 1.95$, $p = 0.18$]. Although PTSD patients and controls did not differ significantly in DF performance, visual inspection suggests that the DF effect was mainly carried by the PTSD group. For recognition bias, no significant main effects or interactions were found and the two groups did not differ significantly in that measure [$F(1, 18) = 0.46$, $p = 0.51$].

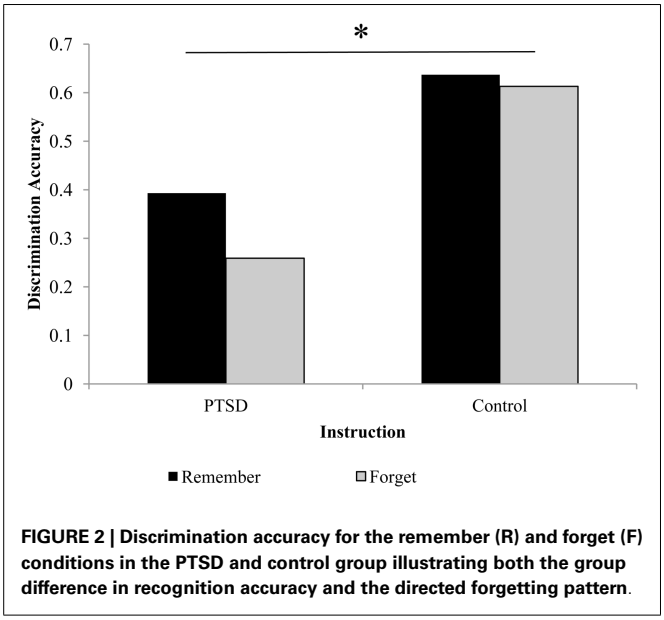


FIGURE 2 | Discrimination accuracy for the remember (R) and forget (F) conditions in the PTSD and control group illustrating both the group difference in recognition accuracy and the directed forgetting pattern.

PICTURE APPRAISAL AND DISSOCIATIVE SYMPTOMS

Overall, participants rated the pictures on the respective nine-point scales as somewhat negative ($M = 3.70$, SD = 0.81), of average arousal ($M = 5.30$, SD = 1.29), and not very trauma relevant ($M = 3.56$, SD = 1.79). Comparing the two groups, there was a trend for the PTSD group to rate the pictures as more negative than the control group [dimension of valence; $t(18) = 1.94, p = 0.068$]. The ratings regarding the other dimensions were similar for the two groups, neither differing in arousal [$t(18) = 1.24$, $p = 0.23$] nor in trauma relevance [$t(18) = -0.61, p = 0.55$].

Considering dissociation, the PTSD group had a mean DES score of 32.6 (SD = 7.32), which was much higher than the control group's [$M = 11.3$, SD = 11.7, $t(18) = 4.55$, $p < 0.001$]. For two participants, the DES could not be administered. These participants' DES scores were therefore substituted by their scores on a similar dissociation questionnaire[3]. Overall, dissociation scores were negatively correlated with ratings of picture arousal ($r = -0.44$, $p = 0.05$) and in tendency also valence ($r = -40$, $p = 0.08$) and the relationship between valence and arousal ratings was well described by a linear relationship [$r = -0.61$, $p < 0.01$; $r^2 = 0.37$, $F(1, 18) = 10.56$, $p < 0.01$] indicating that on average the more negative pictures were not rated as arousing but more positive pictures were rated as also more arousing. The linear relationship between valence and arousal observed in this sample is illustrated in **Figure 3**.

RECOGNITION MEMORY, PICTURE APPRAISAL, AND DISSOCIATIVE SYMPTOMS

ANCOVA revealed that discrimination accuracy differed depending on the perceived valence of the pictures [$F(1, 17) = 6.65$, $p = 0.020$]. Pearson correlations indicated a significant positive association between mean picture valence and discrimination accuracy ($r = 0.59$, $p = 0.007$ for R items; $r = 0.61$, $p = 0.004$ for F-items). As demonstrated in **Figure 4**, the more positive an individual rated the pictures, the higher the discrimination accuracy score. The two groups contributed similarly to this effect: in the PTSD group, the relationship between Pr and valence was $r = 0.56$, $p = 0.15$ for F-items and $r = 0.63$, $p = 0.09$ for R-items. In the control group it was $r = 0.53$, $p = 0.08$ for F-items and $r = 0.46$, $p = 0.13$ for R-items.

Adding mean arousal or trauma relevance ratings, or DES scores as covariates yielded no significant main effects. However, targeted correlation analyses revealed a trend for a positive relationship between DF magnitude ($Pr_R - Pr_F$) and DES scores ($r = 0.43$, $p = 0.061$), the numerical value of which was higher in the PTSD ($r = 0.60$) than control group ($r = 0.18$, both n.s.).

inclusion of these "underestimators" would have reduced hit rates artificially, without shedding more light on the difference between R- and F-items, which was the main research question in this study.

[3]This questionnaire called *Current Dissociation* was developed in the outpatient center and, similarly to the DES, asks for the occurrence of typical dissociative symptoms like blurred vision, out-of-body experiences, etc., in daily life. Since answers are rated on four-point scales, the mentioned two patients' test scores were transformed into a percentage rate (points reached/points possible) to ensure comparability with DES scores.

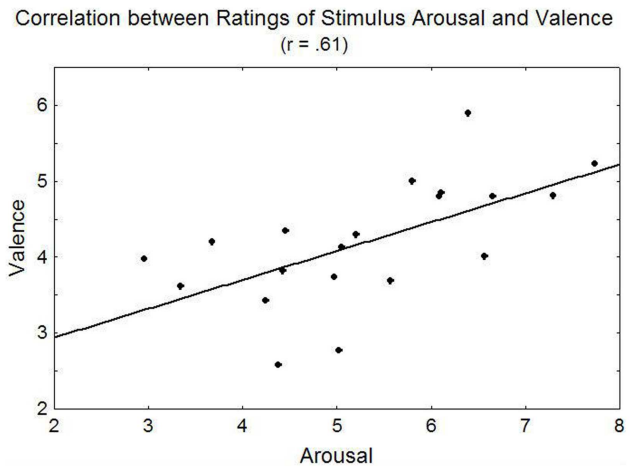


FIGURE 3 | Relationship between valence and arousal ratings in the present sample.

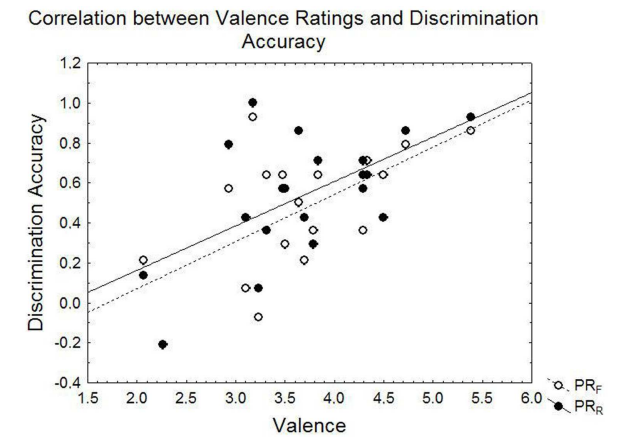


FIGURE 4 | Illustration of the linear correlation between mean valence ratings and discrimination accuracy (Pr). For valence ratings, higher numbers indicate more positive ratings.

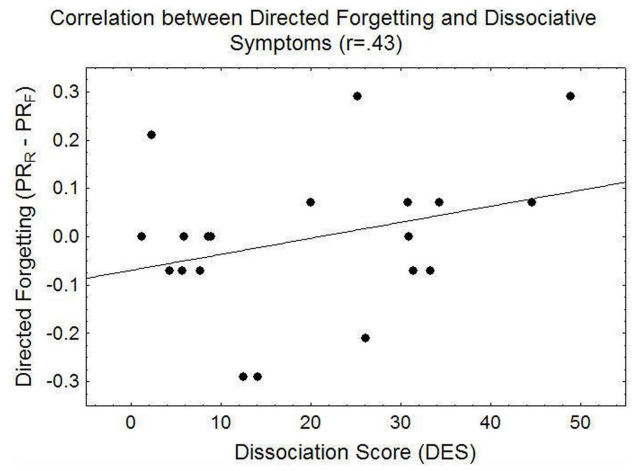


FIGURE 5 | Illustration of the linear correlation between the magnitude of DF (in terms of recognition accuracy Pr) and scores on the dissociative experience scale (DES).

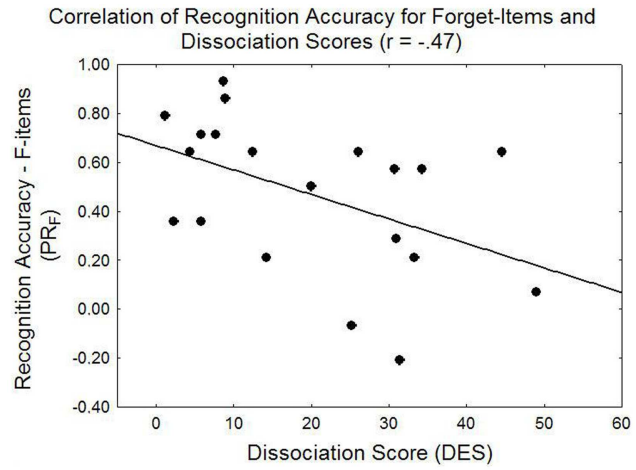


FIGURE 6 | Illustration of the linear correlation between recognition accuracy for to-be-forgotten items and dissociation scores.

In particular, DES scores were negatively correlated with Pr_F, the classification accuracy for F-items ($r = -0.47$, $p < 0.05$), indicating reduced recognition accuracy for F-items, but not R-items ($r = -0.23$, $p = 0.33$) in people with higher DES scores. **Figure 5** displays the overall relationship between directed forgetting and dissociation scores and **Figure 6** specifically illustrates the relationship between recognition accuracy for F-items and dissociation scores.

DISCUSSION

This study investigated item-method DF in a culturally heterogeneous group of traumatized refugees with PTSD, focusing on the role of possible mediating factors such as dissociative symptoms and stimulus appraisal. To this end, an item-method DF task with complex pictorial stimuli was used. Participants' dissociative symptoms and subjective appraisals of stimulus valence, arousal, and trauma relevance were assessed, and these variables' relationship to DF patterns was investigated.

Overall, controls produced more hits than PTSD patients, whereas PTSD patients produced more false alarms than controls, resulting in worse discrimination accuracy in the PTSD group. Consistent with typical DF patterns in recognition memory designs, across groups more false alarms were generated for F-lures than for R lures. Also, the more positively a picture was evaluated, the better it was discriminated. Moreover, participants with more dissociative symptoms had worse recognition of to-be-forgotten pictures and rated the pictures as less arousing and in tendency also more negative.

In the following, we will discuss these results in relation to extant literature and consider further suggestions emerging from

this study: the higher false alarm rate in the PTSD group is consistent with previous reports of higher susceptibility to false memories in traumatized individuals (Bremner et al., 2000; Zoellner et al., 2000; Goodman et al., 2011). Considering hits and false alarms together, the control group's discrimination accuracy was higher than the PTSD group's, reflecting PTSD patients' memory impairment (e.g., Jelinek et al., 2006; McNally, 2006; Brewin et al., 2007) and extending this finding to a ethnically diverse population of immigrant refugees.

The directed forgetting instruction affected memory performance in that a significantly higher number of false alarms for F than R items (Kimball and Bjork, 2002; Zwissler et al., 2011, 2012) and a trend toward higher discrimination accuracy for R- than F-items were found. However, the two groups did not differ significantly in DF performance and if anything, the DF effect appeared to be carried more by the PTSD than by the control group. Several factors might explain this pattern: first, statistical power may have been insufficient as in between-group designs, 26 participants are considered necessary even for large effect sizes, given an α-level of 0.05, to achieve a statistical power of 0.8 (Cohen, 1992). For medium and small effect sizes, 64 and 393 participants would be needed, respectively, clearly many more than took part in the present study and produced useable data. Second, to avoid floor effects in the patient group, this study contained relatively few items and item presentation (4000 ms) was longer than in our previous experiments (Hauswald and Kissler, 2008; Hauswald et al., 2011; Zwissler et al., 2012). This may have fostered encoding of both R- *and* F-items in the non-memory impaired control group, thereby reducing DF. Studies that found a reduction of DF effects with increasing item-cue intervals, support this explanation (Wetzel and Hunt, 1977; Hourihan and Taylor, 2006).

The near ceiling results in the control group could also be attributable to the use of pictorial material. Although several studies (Hauswald and Kissler, 2008; Hauswald et al., 2011; Nowicka et al., 2011; Zwissler et al., 2011, 2012) have found robust DF effects using complex pictures, effects tend to be smaller than those typically found for words (Quinlan et al., 2010). However, pictorial stimuli allow for investigation of culturally and linguistically heterogeneous groups. In the present sample there was no single language all participants spoke.

Regarding the influence of stimulus appraisal on memory, valence ratings were significantly correlated with discrimination accuracy: the more positively the picture set was evaluated, the more accurately the pictures were discriminated. This result fits well with a study on intentional forgetting in children with PTSD that found significantly higher recognition accuracy for positive than negative words (Yang et al., 2010). In the present study PTSD patients tended to rate the pictures more negatively than did controls, which might contribute to their impaired discrimination accuracy. In general, memory for emotionally negative pictures is based more on gist than on detail (Adolphs et al., 2001), but the present design required encoding of details for successful discrimination.

The present study does not indicate that PTSD patients as such have larger DF effects, which is in line with other researchers' failure to observe differences between traumatized participants and controls (e.g., McNally et al., 1998, 2001, 2004). However, participants with higher dissociation scores had lower discrimination accuracies specifically for to-be-forgotten items. Indeed, under the avoidant encoding hypothesis individuals with high dissociation scores should be superior forgetters and thus show reduced memory for F-items. This pattern could be taken as tentative support for a special role of dissociative symptoms in directed forgetting. However, given the small sample and the controversy in the literature (cf. Cloitre et al., 1996; DePrince and Freyd, 2001, 2004; McNally et al., 2001, 2004), this finding needs extension and replication. Participants with higher dissociation scores also rated the stimuli as less arousing and somewhat more negative. This is in line with emotional numbing in dissociation (Frewen and Lanius, 2006) and could also account for the unusual linear relationship between valence and arousal found in the present data. Whereas typically both more negative and more positive stimuli are rated as more arousing, here, this held only for positive stimuli.

PTSD patients have been suggested to differ according to their physiologic and psychological response patterns to trauma reminders, resulting in hyper-aroused and dissociative sub-types (Schauer and Elbert, 2010) and the present results point to possible mnemonic consequences. Also, Moulds and Bryant (2002, 2005) founder larger DF effects in ASD, whose diagnosis requires high-dissociative symptom scores. Although challenging to conduct, a comparison of two large groups of PTSD patients who differ solely in their dissociative versus hyperarousal symptoms would provide a crucial test.

The previous finding of reduced DF for more arousing stimuli, concomitant with higher arousal ratings in PTSD, was not replicated in this study (Zwissler et al., 2012). Whereas several studies found a reduction of item-method DF for arousing stimuli in healthy participants (Yang et al., 2010; Hauswald et al., 2011; Nowicka et al., 2011; Zwissler et al., 2011, 2012), so far no study has systematically assessed the influence of valence and arousal on item-method DF across a wide range of arousal levels in large groups of PTSD patients. As suggested by the present data, emotional appraisal may vary with clinically relevant symptoms such as dissociation. Moreover, potential cultural variations in emotional appraisal are virtually unexplored. Future studies, using a broader range of stimuli, can shed more light on the relationship between valence, arousal, and DF in PTSD. In order to avoid clinical complications such as flashbacks or dissociative fainting during the experiment, the present experiment only used stimuli that were of relatively moderate valence and arousal, limiting statistical power to detect an effect on memory performance. This restriction probably also reduced our ability to identify any influence of "trauma relevance" on our data. Although participants perceived some variation of emotional content in the stimuli, they did not find them particularly representative of their own, often quite atrocious, experiences.

Taken together, results demonstrate reduced discrimination accuracy in PTSD patients, resulting from fewer hits and more false alarms. Data also reveal worse discrimination accuracy for more negatively evaluated stimuli. Participants with more dissociative symptoms exhibited altered stimulus appraisal, rating the stimuli as less emotionally intense. Importantly, individuals with high dissociation scores may indeed be better at directed forgetting. However, this last finding needs further scrutiny in a larger

study, although large samples are difficult to obtain in this population. Traumatized patients typically have many problems related to their trauma, traumatized immigrants in particular also have many problems related to social and cultural factors, which, as such reduce their motivation to take part in scientific studies as well as reduce data quality and interpretability.

Despite these limitations, research on underprivileged samples that receive little attention from scientists and health-care providers, such as refugees with PTSD, is important for science and practice: systematic investigation will reveal typical cognitive phenomena and facilitate their scientific explanation. Identification of functional problems can aid the development of effective treatments. In refugees and migrants from war-torn societies, extremely traumatic experiences and resulting psychological impairments are quite frequent (Gäbel et al., 2006; Kinzie, 2006). Their investigation is essential to understand the characteristics, impairments, and needs of refugees and migrants in order to eventually provide help. The current study took one step toward this goal.

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REFERENCES

Adolphs, R., Denburg, N. L., and Tranel, D. (2001). The amygdala's role in long-term declarative memory for gist and detail. *Behav. Neurosci.* 115, 983–992. doi:10.1037/0735-7044.115.5.983

APA. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn. Arlington, VA: American Psychiatric Publishing, Inc.

Bernstein, E. M., and Putnam, F. W. (1986). Development, reliability, and validity of a dissociation scale. *J. Nerv. Ment. Dis.* 174, 727–735. doi:10.1097/00005053-198612000-00004

Blake, D. D., Weathers, F. W., Nagy, L. M., and Kaloupek, D. G. (1995). The development of a Clinician-Administered PTSD Scale. *J. Trauma Stress* 8, 75–90. doi:10.1002/jts.2490080106

Bremner, J. D., Shobe, K. K., and Kihlstrom, J. F. (2000). False memories in women with self-reported childhood sexual abuse: an empirical study. *Psychol. Sci.* 11, 333–337. doi:10.1111/1467-9280.00266

Brewin, C. R., Kleiner, J. S., Vasterling, J. J., and Field, A. P. (2007). Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. *J. Abnorm. Psychol.* 116, 448–463. doi:10.1037/0021-843x.116.3.448

Cloitre, M., Cancienne, J., Brodsky, B., Dulit, R., and Perry, S. W. (1996). Memory performance among women with parental abuse histories: enhanced directed forgetting or directed remembering? *J. Abnorm. Psychol.* 105, 204–211. doi:10.1037/0021-843x.105.2.204

Cohen, J. (1992). A power primer. *Psychol. Bull.* 112, 155–159. doi:10.1037/0033-2909.112.1.155

DePrince, A. P., and Freyd, J. J. (2001). Memory and dissociative tendencies: the roles of attentional context and word meaning in a directed forgetting task. *J. Trauma Dissociation* 2, 67–82. doi:10.1300/J229v02n02_06

DePrince, A. P., and Freyd, J. J. (2004). Forgetting trauma stimuli. *Psychol. Sci.* 15, 488–492. doi:10.1111/j.0956-7976.2004.00706.x

DePrince, A. P., Freyd, J. J., and Malle, B. F. (2007). A replication by another name: a response to Devilly et al. (2007). *Psychol. Sci.* 18, 218–219. doi:10.1111/j.1467-9280.2007.01876.x

Devilly, G. J., and Ciorciari, J. (2007). Conclusions in science when theory and data collide. *Psychol. Sci.* 18, 220–221. doi:10.1111/j.1467-9280.2007.01877.x

Devilly, G. J., Ciorciari, J., Piesse, A., Sherwell, S., Zammit, S., Cook, F., et al. (2007). Dissociative tendencies and memory performance on directed-forgetting tasks. *Psychol. Sci.* 18, 212–217. doi:10.1111/j.1467-9280.2007.01875.x

Dubester, K. A., and Braun, B. G. (1995). Psychometric properties of the Dissociative Experiences Scale. *J. Nerv. Ment. Dis.* 183, 231–235. doi:10.1097/00005053-199504000-00008

Foa, E. B., Cashman, L., Jaycox, L., and Perry, K. (1997). The validation of a self-report measure of posttraumatic stress disorder: the Posttraumatic Diagnostic Scale. *Psychol. Assess.* 9, 445–451. doi:10.1037/1040-3590.9.4.445

Frewen, P. A., and Lanius, R. A. (2006). Toward a psychobiology of posttraumatic self-dysregulation: reexperiencing, hyperarousal, dissociation, and emotional numbing. *Ann. N. Y. Acad. Sci.* 1071, 110–124. doi:10.1196/annals.1364.010

Frischholz, E. J., Braun, B. G., Sachs, R. G., and Hopkins, L. (1990). The dissociative experiences scale: further replication and validation. *Dissociation* 3, 151–153.

Gäbel, U., Ruf, M., Schauer, M., Odenwald, M., and Neuner, F. (2006). Prävalenz der Posttraumatischen Belastungsstörung (PTSD) und Möglichkeiten der Ermittlung in der Asylverfahrenspraxis. *Z. Klin. Psychol. Psychother.* 35, 12–20. doi:10.1026/1616-3443.35.1.12

Geraerts, E., and McNally, R. J. (2008). Forgetting unwanted memories: directed forgetting and thought suppression methods. *Acta Psychol. (Amst.)* 127, 614–622. doi:10.1016/j.actpsy.2007.11.003

Goodman, G. S., Ogle, C. M., Block, S. D., Harris, L. S., Larson, R. P., Augusti, E.-M., et al. (2011). False memory for trauma-related Deese-Roediger-McDermott lists in adolescents and adults with histories of child sexual abuse. *Dev. Psychopathol.* 23, 423–428. doi:10.1017/s0954579411000150

Hauswald, A., and Kissler, J. (2008). Directed forgetting of complex pictures in an item method paradigm. *Memory* 16, 797–809. doi:10.1080/09658210802169087

Hauswald, A., Schulz, H., Iordanov, T., and Kissler, J. (2011). ERP dynamics underlying successful directed forgetting of neutral but not negative pictures. *Soc. Cogn. Affect. Neurosci.* 6, 450–459. doi:10.1093/scan/nsq061

Hourihan, K. L., and Taylor, T. L. (2006). Cease remembering: control processes in directed forgetting. *J. Exp. Psychol. Hum. Percept. Perform.* 32, 1354–1365. doi:10.1037/0096-1523.32.6.1354

Jelinek, L., Jacobsen, D., Kellner, M., Larbig, F., Biesold, K.-H., Barre, K., et al. (2006). Verbal and nonverbal memory functioning in posttraumatic stress disorder (PTSD). *J. Clin. Exp. Neuropsychol.* 28, 940–948. doi:10.1080/13803390591004347

Johnson, H. M. (1994). Processes of successful intentional forgetting. *Psychol. Bull.* 116, 274–292. doi:10.1037/0033-2909.116.2.274

Kimball, D. R., and Bjork, R. A. (2002). Influences of intentional and unintentional forgetting on false memories. *J. Exp. Psychol. Gen.* 131, 116–130. doi:10.1037/0096-3445.131.1.116

Kinzie, J. D. (2006). Immigrants and refugees: the psychiatric perspective. *Transcult. Psychiatry* 43, 577–591. doi:10.1177/1363461506070782

Korfine, L., and Hooley, J. M. (2000). Directed forgetting of emotional stimuli in borderline personality disorder. *J. Abnorm. Psychol.* 109, 214–221. doi:10.1037/0021-843x.109.2.214

Lindert, J., Brähler, E., Wittig, U., Mielck, A., and Priebe, S. (2008). Depressivität, Angst und Posttraumatische Belastungsstörung bei Arbeitsmigranten, Asylbewerbern und Flüchtlingen – Systematische Übersichtsarbeit zu Originalstudien. *Psychother. Psychosom. Med. Psychol.* 58, 109–122. doi:10.1055/s-2008-1067358

McNally, R. J. (2006). Cognitive abnormalities in post-traumatic stress disorder. *Trends Cogn. Sci. (Regul. Ed.)* 10, 271–277. doi:10.1016/j.tics.2006.04.007

McNally, R. J., Clancy, S. A., Barrett, H. M., and Parker, H. A. (2004). Inhibiting retrieval of trauma cues in adults reporting histories of childhood sexual abuse. *Cogn. Emot.* 18, 479–493. doi:10.1080/02699930341000400

McNally, R. J., Clancy, S. A., and Schacter, D. L. (2001). Directed forgetting of trauma cues in adults reporting repressed or recovered memories of childhood sexual abuse. *J. Abnorm. Psychol.* 110, 151–156. doi:10.1037/0021-843x.110.1.151

McNally, R. J., Metzger, L. J., Lasko, N. B., Clancy, S. A., and Pitman, R. K. (1998). Directed forgetting of trauma cues in adult survivors of childhood sexual abuse with and without posttraumatic stress disorder. *J. Abnorm. Psychol.* 107, 596–601. doi:10.1037/0021-843x.107.4.596

McNally, R. J., Ristuccia, C. S., and Perlman, C. A. (2005). Forgetting of trauma cues in adults reporting continuous or recovered memories of childhood sexual abuse. *Psychol. Sci.* 16, 336–340. doi:10.1111/j.0956-7976.2005.01536.x

Moulds, M. L., and Bryant, R. A. (2002). Directed forgetting in acute stress disorder. *J. Abnorm. Psychol.* 111, 175–179. doi:10.1037/0021-843x.111.1.175

Moulds, M. L., and Bryant, R. A. (2005). An investigation of retrieval inhibition in acute stress disorder. *J. Trauma Stress* 18, 233–236. doi:10.1002/jts.20022

Nowicka, A., Marchewka, A., Jednorog, K., Tacikowski, P., and Brechmann, A. (2011). Forgetting of emotional information is hard: an fMRI study of directed forgetting. *Cereb. Cortex* 21, 539–549. doi:10.1093/cercor/bhq117

Quinlan, C. K., Taylor, T. L., and Fawcett, J. M. (2010). Directed forgetting: comparing pictures and words. *Can. J. Exp. Psychol.* 64, 41–46. doi:10.1037/a0016569

Schauer, M., and Elbert, T. (2010). Dissociation following traumatic stress: etiology and treatment. *Z. Psychol.* 218, 109–127. doi:10.1027/0044-3409/a000018

Terr, L. (1994). *Unchained Memories: True Stories of Traumatic Memories, Lost and Found.* New York, NY: Basic Books.

Wetzel, C. D., and Hunt, R. E. (1977). Cue delay and the role of rehearsal in directed forgetting. *J. Exp. Psychol. Hum. Learn. Mem.* 3, 233–245. doi:10.1037/0278-7393.3.2.233

Yang, H.-B., Wang, Y.-Y., Bai, X.-J., Wen, Y.-X., and Chen, Z.-Y. (2010). Influence of emotional state on intentional forgetting of PTSD children after earthquake. *Chin. J. Clin. Psychol.* 18, 600–603.

Zoellner, L. A., Foa, E. B., Brigidi, B. D., and Przeworski, A. (2000). Are trauma victims susceptible to "false memories"? *J. Abnorm. Psychol.* 109, 517–524. doi:10.1037/0021-843x.109.3.517

Zoellner, L. A., Sacks, M. B., and Foa, E. B. (2003). Directed forgetting following mood induction in chronic posttraumatic stress disorder patients. *J. Abnorm. Psychol.* 112, 508–514. doi:10.1037/0021-843x.112.3.508

Zwissler, B., Hauswald, A., Koessler, S., Ertl, V., Pfeiffer, A., Wöhrmann, C., et al. (2012). Memory control in post-traumatic stress disorder: evidence from item method directed forgetting in civil war victims in Northern Uganda. *Psychol. Med.* 42, 1283–1291. doi:10.1017/S0033291711002273

Zwissler, B., Koessler, S., Engler, H., Schedlowski, M., and Kissler, J. (2011). Acute psycho-social stress does not disrupt item-method directed forgetting, emotional stimulus content does. *Neurobiol. Learn. Mem.* 95, 346–354. doi:10.1016/j.nlm

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Overexpression of mineralocorticoid receptors does not affect memory and anxiety-like behavior in female mice

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Mineralocorticoid receptors (MRs) have been implicated in behavioral adaptation and learning and memory. Since—at least in humans—MR function seems to be sex-dependent, we examined the behavioral relevance of MR in female mice exhibiting transgenic MR overexpression in the forebrain. Transgenic MR overexpression did not affect contextual fear memory or cued fear learning and memory. Moreover, MR overexpressing and control mice discriminated equally well between fear responses in a combined cue and context fear conditioning paradigm. Also context-memory in an object recognition task was unaffected in MR overexpressing mice. We conclude that MR overexpression in female animals does not affect fear conditioned responses and object recognition memory.

Keywords: fear, memory, mineralocorticoid receptor, hippocampus, sex, anxiety

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Introduction

Exposure to stressful experiences activates the Hypothalamus-Pituitary-Adrenal (HPA)-axis, which—among other things—results in elevated plasma levels of corticosteroid hormones (corticosterone in rodents, cortisol in humans; Joels and Baram, 2009). Corticosteroids bind to two types of corticosteroid receptors: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), which differ in their localization in the brain and affinity for corticosterone (Reul and de Kloet, 1985; de Kloet et al., 2005). Both MRs and GRs can exert slow genomic actions on cellular function, but recent studies have demonstrated that activation of these receptors can also activate fast membrane receptor mediated non-genomic pathways (Di et al., 2003; Karst et al., 2005, 2010; Groc et al., 2008; Groeneweg et al., 2011).

In male rodents, corticosterone acting via MRs facilitates spatial learning (Berger et al., 2006; Lai et al., 2007), reduces anxiety (Lai et al., 2007; Rozeboom et al., 2007) and improves the formation of contextual fear (Zhou et al., 2011). Moreover, MR activation regulates the selection of appropriate behavioral strategies in the face of stress, favoring a switch from hippocampus-dependent to striatal learning strategies (Schwabe et al., 2010, 2013). Overall, these studies in rodents suggest that MR activation favors behavioral adaptation to stressful events.

Also in humans, MRs are important for neuroendocrine function and behavioral adaptation (DeRijk et al., 2006; Otte et al., 2015). Two single-nucleotide polymorphisms (SNPs) of the human

MR gene (*−2G/C* and *I180V*) have been associated with variability in MR functionality. Specifically, a common haplotype involving these SNPs (MR-2C/MRI180) was associated with high MR expression and trans-activational activity *in vitro* (van Leeuwen et al., 2011). Individuals carrying this haplotype also displayed high salivary and plasma cortisol responses in a psychosocial stress situation (van Leeuwen et al., 2011). Homozygous female but not male carriers of haplotype 2 were found to have higher dispositional optimism, fewer thoughts of hopelessness and a lower risk on major depression (Klok et al., 2011).

Thus, in general MRs seem to enhance behavioral adaptation to stressful events, facilitate (fear) learning and memory, and promote resilience to stressful events (de Kloet et al., 2005). However, most studies that specifically investigated learning and memory in rodents so far focused on the MR in males; relatively little is known about the effect of (enhanced) MR function in females (ter Horst et al., 2013; Arp et al., 2014). Since sex-differences in MR function appear to exist in humans and rodents, we examined in this study whether forebrain-specific overexpression of MRs in female mice affects contextual memory formation, emotional memory formation and anxiety.

Materials and Methods

Animals

All mice used in our experiments were bred in-house. In each breeding cage, two wild type C57Bl6 female mice (Harlan, The Netherlands) were housed with one MR-transgenic (MR-tg) male mouse (Lai et al., 2007) for 1 week. Subsequently, the male mice were removed and the female mice were left undisturbed until day 18 of their pregnancy. From this point in time, the female mice were individually housed until they gave birth. We preferred to use wild type rather than MR-tg dams, to keep maternal care as comparable as possible to earlier studies in C57Bl6 mice. At postnatal day (PND) 23, all pups were weaned, genotyped and female pups with identical genotypes were housed four per cage. Mice were left undisturbed (except for cage cleaning once a week) until testing, when they were 3–3.5 months of age.

Mice were kept in a temperature and humidity controlled facility (21.5–22°C with humidity between 40 and 60%) on a 12 h light/dark cycle (lights on at 8:00 a.m.) with food and water available *ad libitum*. All experiments were performed in accordance with the Dutch regulations for animal experiments (DED206).

Body Weights and Basal Corticosterone Levels

The body weight of the mice was recorded before the initiation of behavioral testing. Two weeks after the completion of the behavioral test, mice were decapitated in the morning between 09:00 and 11:00 h and their trunk blood was collected in Ethylenediaminetetraacetic acid (EDTA)-covered capillary tubes (Sarstedt, Netherlands) to determine basal plasma corticosterone levels. These levels were measured in duplicate via a radioimmunoassay kit according to the manufacturer's protocol (MP Biochemicals, Amsterdam, Netherlands).

Behavior

We performed all behavioral tests during the light phase between 8:30 a.m. and 12:00 a.m. We used a different cohort of mice for each of the behavioral tests: (i) object-in-context recognition memory; (ii) contextual fear conditioning; (iii) cued fear conditioning; and (iv) combined cued and context conditioning. All four different cohorts of mice were first tested on the elevated plus maze at 3 months of age and 1 week later subjected to one of the behavioral tests listed above.

Elevated Plus Maze (EPM)

Mice were transferred from the housing room to the behavior testing room 30 min before the actual testing. The mouse was placed in the center of a plus maze (light gray plexiglass; open arms: length 36.5 cm, width 0.5 cm; closed arm: length 35.2 cm, width 0.5 cm, side walls: 15.0 cm; elevation poles: 58.5 cm, UGO BASILE S.r.l.—Italy). The maze was cleaned with 70% ethanol and dried thoroughly with paper tissue before the mouse was placed in the maze. At the start of the test, each mouse faced the same open arm. After 5 min of testing the mouse was removed from the plus maze and returned to its home cage. A camera above the maze was used to record the sessions. The videos were analyzed by Ethovision XT 6 (Noldus, Wageningen, Netherlands). We estimated the percentage of time spent in the open arm and the number of open arm entries; low values are considered to reflect anxiety-like behavior. The total distance moved in the maze (open and closed arms) was used as an indication of general locomotor activity.

Contextual Fear Conditioning

Contextual fear memory was examined as described before (Zhou et al., 2011). On day 1, the mouse was placed in a chamber (W × L × H: 25 cm × 25 cm × 30 cm) that had a stainless steel grid floor connected to a shock generator. After 3 min of free exploration a single foot shock of 0.4 mA was delivered for 2 s. 30 s later the mouse was removed from the chamber and returned to its home cage. On day 2, the mouse was placed in the same chamber for 3 min. The occurrence of freezing behavior [defined as no body movements except those related to breathing Zhou et al. (2009, 2010)] was checked and scored every 2 s on days 1 and 2. For analysis we calculated for each day the total time spent freezing as a percentage of the total duration of the test.

Cued Fear Conditioning

Cued fear conditioning was examined to assess amygdala-dependent (fear) memory formation. On day 1, the mouse was placed in a black chamber (W × L × H: 25 cm × 25 cm × 30 cm), that had a stainless steel grid floor connected to a shock generator (Context A). The mouse could freely explore this chamber for 3 min. Thereafter, a tone (100 dB, 2.8 kHz) was given, lasting 30 s; during the last 2 s the mouse received a single foot shock of 0.4 mA. Thirty seconds later, the mouse was returned to its home cage. Twenty-four hours later on day 2, the mouse was placed in another chamber with striped patterns on the walls and a smooth

floor (Context B) and allowed to explore for 3 min. Thereafter, the same tone as on day 1 but without shock was delivered for 30 s; the mouse remained in this chamber for another 30 s before being returned to its home cage. Before each mouse was tested, chambers were cleaned: Context A with 70% ethanol and Context B with 1% acetic acid, providing also different smells to the environments. Freezing behavior of the mouse was scored every 2 s (see above). The analysis was performed by the same investigator as the one carrying out the behavioral test but blinded to the experimental groups during analysis.

Combined Cued and Context Conditioning

On day 1, the mouse was placed in a fear conditioning chamber (W × L × H: 25 cm × 25 cm × 30 cm) that was cleaned with 70% ethanol. The grid floor was made of stainless-steel rods and was connected to a shock generator (0.4 mA). A white light source and a camera were placed 20 cm above the chamber. An audio-speaker was connected to a tone generator and positioned on the wall of the chamber. During acquisition (day 1) the mouse was allowed to freely explore the chamber for 3 min. Then, the animal was exposed to six light/tone episodes (cue-on episodes; 20 s each) paired with a foot shock (0.4 mA) during the last 2 s. The interval between the light/tone + shock pairings was 1 min (the context, cue-off episode). Two minutes after the last pairing, mice were returned to their home cage. On day 3 (48 h later), the mouse was exposed to the same procedure as on day 1, but without shocks. Frequency and duration of freezing behavior was scored using Observer XT, Noldus, Wageningen, Netherlands. Freezing behavior was determined and quantified during cue on periods and cue off periods (i.e., after the foot shock) and was defined as no body movements except those related to respiration. This fear conditioning paradigm allowed a test of fear related behavior of the mice during alternating cue-on (light + tone together) and context (cue-off) episodes (Brinks et al., 2009) in the same experimental protocol, thereby enabling detection of generalization and specificity of fear.

Object-in-Context Recognition Memory

We tested the mice for place memory, a non-stressful behavioral task, to examine the influence of context on object recognition (Dix and Aggleton, 1999; Mumby et al., 2002; Eacott and Norman, 2004; O'Brien et al., 2006; Balderas et al., 2008; Spanswick and Sutherland, 2010; Spanswick and Dyck, 2012; Barsegyan et al., 2014). As context we used four blue-colored plastic boxes of identical measurements (W × L × H; 33 cm × 54 cm × 37 cm) with or without visual cues on the walls. The boxes contained bedding material and additional objects: blocks of Lego and/or small bottles.

Mice were tested on three subsequent days. On day 1, the mouse was placed for 10 min in a box with no wall cues and without objects. On day 2, the mouse was placed for 10 min in a box (context A) that had no cues on the walls but contained two identical objects, i.e., two blocks of Lego, placed in opposite corners. Thereafter, the mouse was placed for 10 min into another box (context B) with cues on the walls in the form of stripes and two (new) identical objects, i.e., 2 small bottles, placed in opposite corners. Between exposure to context A and context B, the mouse was returned to its own transport cage. On day 3 object-in-context recognition memory was tested by placing the mouse for 10 min in context B. Context B on day 3 contained one object which also belonged to context B on day 2 (i.e., familiar object to Context B), and one object which belonged to Context A on day 2 (i.e., unfamiliar object to context B, **Figures 6A–C**). We calculated the discrimination index (DI) on day 3 as a measure for object-in-context recognition memory. The DI was calculated as time spent with the novel object compared to the total exploration time of both objects [t_{novel} /(t_{novel+} $t_{familiar-}$); Mumby et al., 2002; Akkerman et al., 2012]. All objects were cleaned thoroughly between tests, and placed at a 15 cm distance from the corners of the box. Fresh bedding material was added on top of the old and mixed between each session. Sniffing was scored as object-exploration behavior if the mouse displayed such behavior towards an object within a distance of 2 cm maximum. Climbing on top of or "watching" the objects from a (close) distance was not considered as sniffing behavior.

Determination of the Cycle Stage

To take the cycle stage of the females into account, vaginal smears were taken immediately after each behavioral test using a smear loop (size 1 μl; Greiner Bio-one). Cells were transferred on a water drop on a glass microscope slide. Slides were allowed to dry overnight followed by Giemsa (Sigma) staining for 12 min.

Statistical Analysis

Because all data were normally distributed, as determined by Shapiro-Wilk tests for normality (results not shown), we used parametric statistics. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS): two-tailed *t*-test when two means were compared; repeated-measures Analysis of Variance (ANOVA; when appropriate); and two-tailed paired *t*-test (averaged cue and context fear conditioning episodes).

We analyzed the results of the contextual fear conditioning and elevated plus maze task for each cycle stage, because the relatively large number of animals allowed subgroup analysis. For these tests we did not observe any consistent influence of the cycle in the behavioral performance (data not shown). In the other tasks subgroup analysis was not possible due to the rather low number of females in some stages of the cycle. We therefore grouped all stages in the results and tested the impact of cycle stage on behavioral performance with a General Linear Model analysis, including the cycle stage as a covariate.

A $p < 0.05$ was set as the level of significance (∗) and a $p < 0.10$ was considered as a trend level (#). Data are presented as mean with standard error of the mean (SEM), with group size (n) indicated.

Results

Body Weights and Basal Corticosterone Levels

Body weight was measured from all animals before the start of the behavioral paradigms when animals were approximately 3.5 months of age. Female MR-tg mice were found to be significantly heavier in absolute body weight compared to control littermates ($t_{(69)} = -7.92$, $p < 0.001$; **Figure 1A**). MR-tg mice also displayed

a trend towards significantly lower basal plasma corticosterone levels ($t_{(33)} = 1.98$, $p = 0.055$; **Figure 1B**).

Elevated Plus Maze

We tested control and MR-tg female mice at PND 90 with respect to frequency of open arm entries, percentage of time in the open arms and total distance the mice traveled in the elevated plus maze (EPM), for a total duration of 5 min (**Figure 2**). The frequency of open arm entries was similar for control and MR-tg mice ($t_{(70)} = 0.19$, $p = 0.844$). Control and MR-tg mice also spent a comparable amount of time in the open arms ($t_{(70)} = 0.19$, $p = 0.844$). Finally, the general locomotor activity was not different between control and MR-tg animals ($t = 70 = -0.25$, $p = 0.799$).

Contextual Fear Conditioning

During training and prior to the foot shock, MR-tg and control mice displayed little freezing behavior; the percentage of time was comparable for both groups (**Figure 3A**). During the retention test, twenty-four hours later, mice of both groups spent approximately 30% freezing of the total 3 min testing time (data not shown). Since MR is thought to be involved in early appraisal of fear, we distinguished between the first and second half of the observation period, as described before (Zhou et al., 2010). Dividing this period into two blocks of 1.5 min (Zhou et al., 2010) revealed that MR-tg and control mice displayed no differences in the percentage of time freezing ($F_{(1,52)} = 0.086$, $p = 0.770$; **Figure 3B**).

Cued Fear Conditioning

During training, MR-tg and control mice displayed little freezing behavior before exposure to the tone and foot shock (**Figure 4A**). Exposure to the tone increased freezing behavior and freezing behavior was also increased after exposure to the foot shock, in a comparable manner for both groups (**Figure 4A**). Twenty-four hours later, both groups showed similar freezing levels both before and after the presentation of the cue exposure to the tone, now presented in a novel context ($F_{(1,22)} = 1.087$, $p = 0.315$; **Figure 4B**).

Combined Cue and Context Conditioning

The combined cue and context fear conditioning paradigm allows detection of generalization and specificity of fear (Brinks et al., 2009). During acquisition (day 1) both MR-tg mice and wild type littermates increased freezing behavior during cue on and cue off periods ($F_{(11,341)} = 76.761$, $p < 0.001$), and always showed more freezing behavior during the cue off (i.e., after the footshock) when compared to the cue on period (**Figures 5A,B**), as described earlier for this particular paradigm (Brinks et al., 2008, 2009). No significant differences between MR-tg mice and control mice were seen. Fourty-eight hours after training, both control and MR-tg mice displayed freezing behavior during the cue on (**Figure 5C**) and cue off (**Figure 5D**) periods. Animals kept freezing in response to the tone (**Figure 5C**), while showing a decline in freezing behavior during the cue off periods (**Figure 5D**). As a result, animals started freezing less during cue off than during cue on after the fourth cue on exposure ($t_{(36)} = -5.134$, $p < 0.0001$; **Figures 5C,D**). No group differences were observed.

Object-in-Context Recognition Memory

In the object-in-context memory test, mice displayed a preference for the unfamiliar object-context combination (i.e., mice displayed more exploration towards the object not previously explored in context B). Overall, the DI was higher than the chance level of 0.5 (**Figure 6D**). However, statistical analysis revealed no significant differences in the recognition memory between control and MR-tg female mice ($t_{(26)} = 1.700$, $p = 0.101$).

Discussion

MRs have been implicated in orchestrating behavioral responses to stressful experiences (de Kloet et al., 1999; Schwabe et al.,

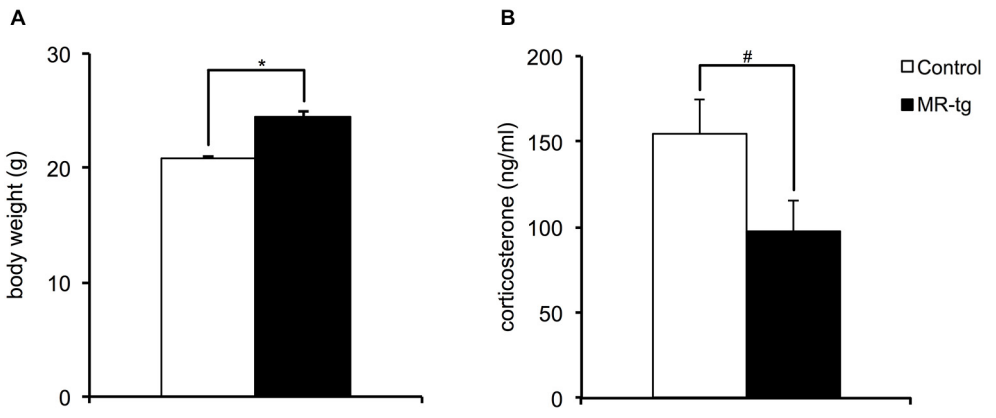


FIGURE 1 | Neuroendocrine parameters. (A) Body weight measured before the initiation of behavioral testing revealed that female MR-tg mice weigh significantly more than control mice. n = 20–24 per group. **(B)** Basal a.m. plasma corticosterone levels measured 2 weeks after the behavioral paradigms showed that MR-tg mice show a trend towards significantly lower basal corticosterone levels than control female mice. n = 15–20 per group. $^{*}p < 0.05$, $^{\#}$trend, $p < 0.10$.

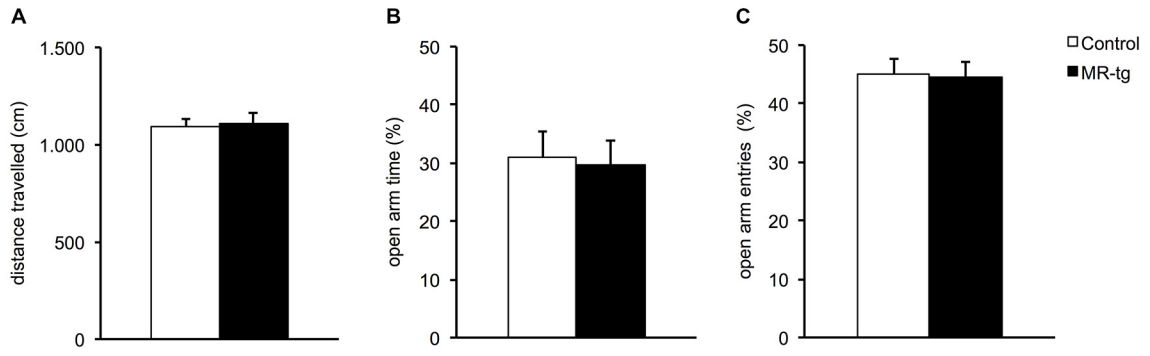


FIGURE 2 | Effects of MR overexpression in elevated plus maze. (A) Forebrain MR overexpression did not alter locomotor activity in MR-tg vs. control female mice. **(B,C)** MR-tg and control mice exhibited no differences in anxiety-like behavior, as the percentage of time in the open arms **(B)** (out of all arm entries) and the percentage of open arm entries **(C)** were similar for both groups. *n* = 35–37 per group.

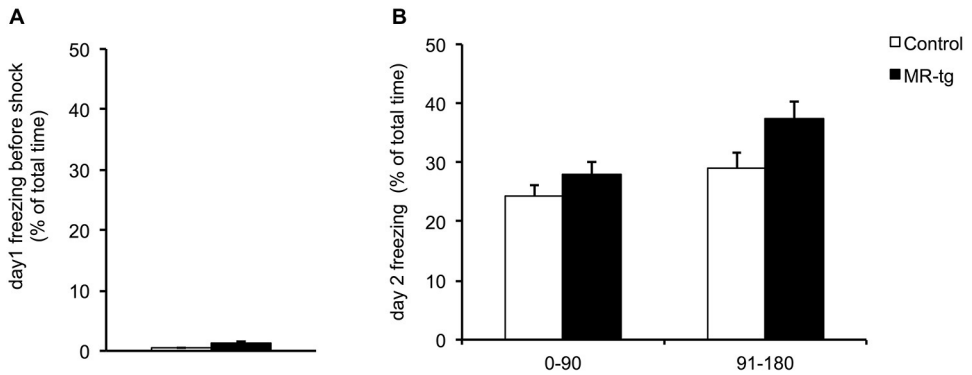


FIGURE 3 | Effects of MR overexpression on contextual fear conditioning. (A) During training, female MR-tg and control mice exhibited no differences in freezing behavior in response to the context, measured for the total 3 min period of testing. **(B)** Twenty-four hours later, MR-tg mice show comparable freezing behavior compared to control mice, when tested over time (first 90 s compared to the last 90 s of time freezing). *n* = 25–30 per group.

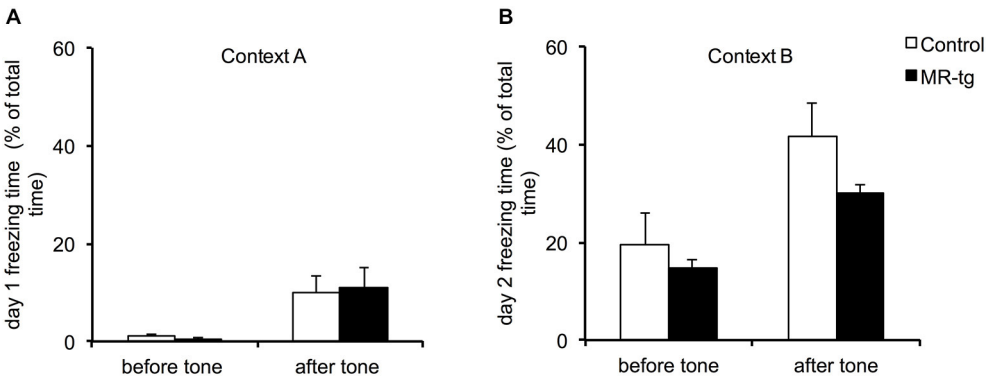


FIGURE 4 | Effects of MR overexpression on cue fear conditioning. (A) During training, comparison between MR-tg and control mice revealed no differences in freezing behavior before as well as after the presence of the tone. **(B)** Twenty-four hours later, both MR-tg and control mice showed similar freezing behavior in response to the new context, when compared before and after the tone presentation. *n* = 8 per group.

2010). This was, for instance, evident by using pharmacological and transgenic manipulations in mice (Schwabe et al., 2010; Arp et al., 2014). Interestingly, higher functionality of MR in humans has been related to higher dispositional optimism, fewer thoughts of hopelessness and a lower risk on major depression (Kuningas et al., 2007; Klok et al., 2011). Yet, this effect was only observed in women (and not men) who display a haplotype related to high MR expression.

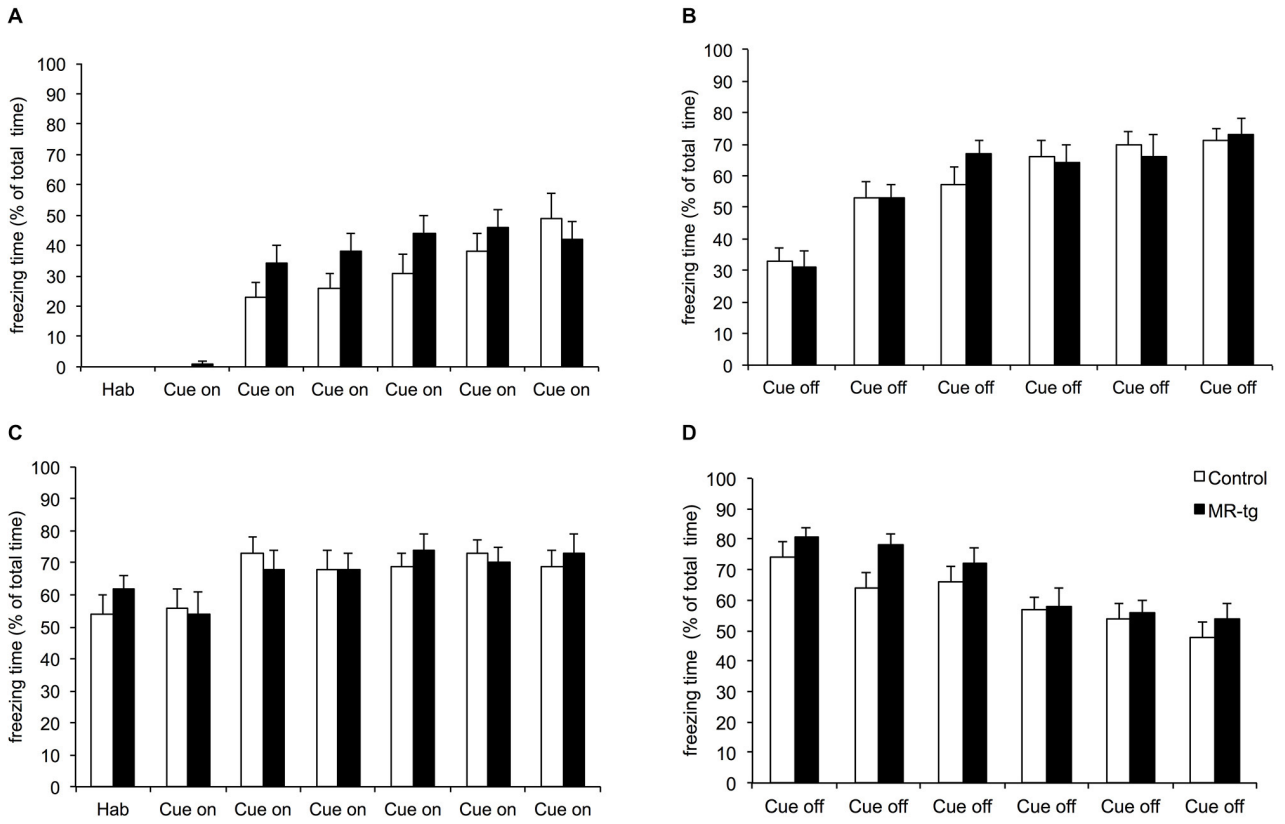


FIGURE 5 | Effects of MR overexpression on combined cue and context conditioning. On the acquisition (day 1), animals were exposed to six tones followed by a foot shock. **(A)** Freezing behavior was scored during the tone (cue on) and after the tone (cue off) **(B)**. Forty-eight hours later mice were exposed to the same procedure as on day 1, but without shocks. Freezing behavior was scored during the tone (cue on) **(C)** and after the tone (cue off) **(D)**. No group differences were observed. n = 15–18 mice per group.

Translating these findings from humans into rodent models, we expected MR overexpression in female mice to reduce anxiety-like behavior, increase fear memory formation and context-depend memory formation. However, we report that MR-tg are highly comparable to their control littermates with regard to anxiety-like behavior, contextual memory formation as well as contextual and cued fear learning, at least in the paradigms we employed in this study.

Characteristics of MR Overexpression in Female Mice

To examine the role of MRs in anxiety and memory formation we used transgenic mice with forebrain specific overexpression of human MR under the control of a calcium/calmodulin-dependent protein kinase II alpha (CaMKIIα) promoter (Lai et al., 2007). Lai et al. (2007) verified the increased MR mRNA levels and reported a 3–4 folds MR mRNA increase in the hippocampus and 8-fold increase in amygdala.

Female mice secrete larger amounts of corticosterone than male animals, both under basal conditions as well as after stress-exposure (Kitay, 1961; Critchlow et al., 1963; Figueiredo et al., 2002; Kitraki et al., 2004; ter Horst et al., 2012). In agreement, we found high levels of basal plasma corticosterone levels in our wild type littermates. Female mice with transgenic overexpression of MRs in the forebrain displayed a tendency towards reduced basal corticosterone levels when compared to wild types although this did not reach significance, perhaps due to the large variation observed especially in the MR-tg animals. This suggests that MR overexpression possibly causes a compensatory down-regulation of corticosterone levels. If so, this potentially stabilizes anxiety and conditioned-fear levels in female animals, since these parameters have been reported to depend on circulating corticosterone levels, at least in male rodents (see e.g., Pugh et al., 1997). These findings on corticosterone levels in females only partially support earlier findings in male mice, i.e., that forebrain-specific genetic modifications resulting in altered MR expression do not consistently affect basal corticosterone levels (Berger et al., 2006; Lai et al., 2007).

Unconditioned Anxiety

Our data show that the forebrain-specific overexpression of MR in female mice has no effect on general anxiety-like behavior as tested in the elevated plus maze. MR-tg and control littermates spent comparable time in the open arms, and had

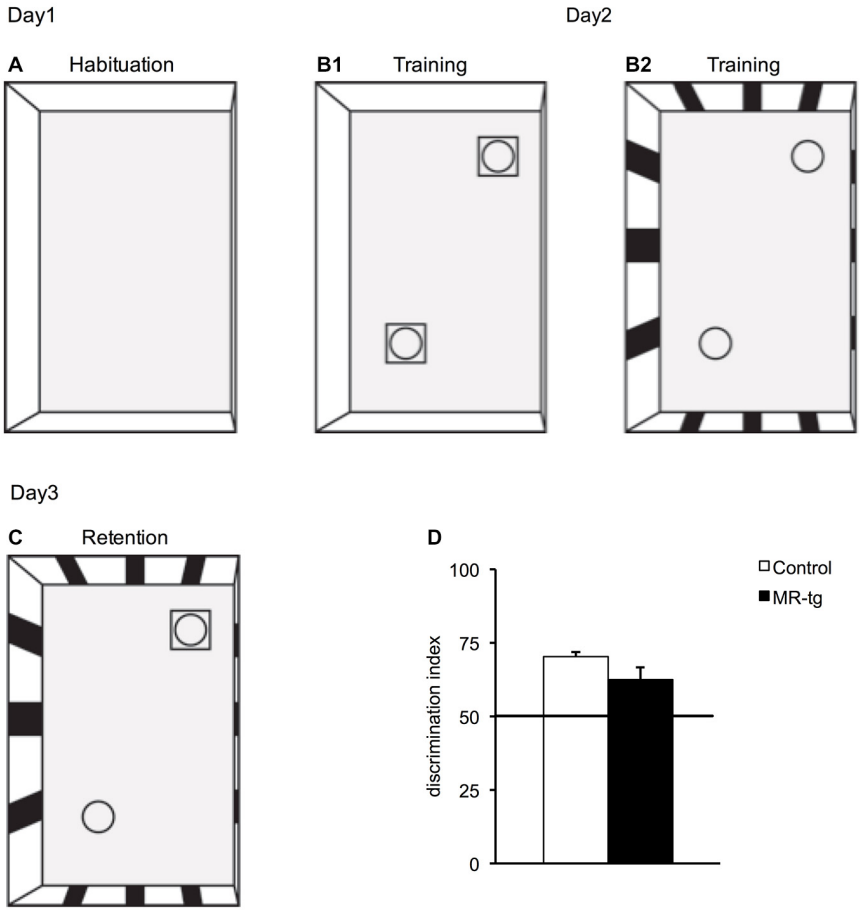


FIGURE 6 | Effects of MR overexpression in object-in context. (A–C) Schematic representation indicating the setup of the object-in-context experimental paradigm: **(A)** On day1, mice were initially habituated in context A that had no objects. **(B1)** On day2, during training, mice were placed in the same context (context A) but with two identical objects and then placed in a novel context (context B) with two identical novel objects **(B2)**. **(C)** On day3, the mice were placed in the context B but with one object being replaced by an object from the first context. **(D)** MR-tg and control mice exhibited no differences when tested for recognition memory of a novel object in the context B, as the discrimination index (DI) of MR-tg mice was not significantly different from that of the control mice. n = 14 per group.

a similar locomotor activity. This does not seem to be specific for female MR-tg mice, since we also observed comparable anxiety-like behavior in the same line of male MR-tg mice and their littermates (Kanatsou et al., unpublished observation). Two earlier studies did report that MR overexpression, in males, reduced anxiety-like behavior in the open field (Lai et al., 2007) or elevated plus maze (Rozeboom et al., 2007). This suggests that sex-dependent differences e.g., in brain circuits related to anxiety behavior could possibly explain the disparity between the earlier and our current observations. Yet, Rozeboom et al. (2007) also reported reduced anxiety-like behavior in female MR-tg mice, as determined in the elevated plus maze, in a highly comparable paradigm as we presently used. It should be pointed out that we took the cycle stage into account, which supposedly was not done in the earlier study (Rozeboom et al., 2007); this may have leveled out putative effects of MR overexpression in our study. In addition, methodological differences between the current study and earlier studies, such as the type of genetic modification, the age of the animals or the type of tests used to assess anxiety, may have contributed to the differences. For instance, we used 3 months old female mice while in earlier studies either age was not reported or animals were tested at a much older age (4–7 months), when phenotypes may have become more prominent (Berger et al., 2006; Lai et al., 2007; Rozeboom et al., 2007). We conducted *post hoc* a power analysis to determine optimal sample size to assure an adequate power to detect statistical significance. Based on this analysis, a large number of female mice (>60) would be required to reach statistical significant differences between the MR-tg and control mice. Therefore, we tentatively conclude that the current experimental conditions do not support a reduction of anxiety in female MR overexpressing mice.

Fear Conditioning of Context and Cue

In contextual and cue fear conditioning, MR-tg female mice displayed comparable levels of freezing when compared to control animals. Studies in male animals reported that MR

blockade impairs contextual (but not cued) fear memory (Zhou et al., 2010) while MR-overexpression enhances contextual fear (Kanatsou et al., unpublished observation). One possible explanation for the lack of effect in females might be that freezing had reached a ceiling, preventing a potential enhancement of contextual and cued memories by overexpression of MRs to be discernable. Interestingly, freezing levels in male MR-tg and wildtype mice were overall lower than in females (Kanatsou et al., unpublished observation), which indirectly supports the ceiling effect explanation. MR overexpression also did not affect fear memory (expressed by freezing) in a combined cue and context fear conditioning paradigm which tests the ability of animals to discriminate between a highly fearful cue-on and the "more safe" situation of cue-off. Therefore, we conclude that also the discriminative ability is not affected by overexpression of MR in female mice.

Memory in a Non-Aversive Context

Pharmacological interventions and transgenic mouse models reducing or blocking the function of MR demonstrated impaired spatial memory in male individuals while non-spatial memory appeared to be intact (Yau et al., 1999; Berger et al., 2006). MR-deficient female mice were earlier reported to have impaired spatial as well as impaired stimulus-response strategies while MR overexpressing females showed improved spatial performance but no changes with respect to stimulus-response behavior (Arp et al., 2014). The latter might be explained by the fact that control littermates of MR-tg mice performed extremely well in the stimulus-response task, preventing further improvement in MR-tg mice (Arp et al., 2014). Here we report that MR overexpression did not affect memory formation in a non-aversive contextual learning task. Also here possible differences could have remained unnoticed due to a potential ceiling effect. This explanation, however, does not seem likely, given the DI-values in control mice, which were significantly but not dramatically above chance level.

Conclusion

Taken together, testing female mice with forebrain-specific MR overexpression in several behavioral tasks revealed no effect on unconditioned anxiety, fear memory, the ability to discriminate between the threatening cue and the relatively safe cue-off period, and non-aversive contextual memory formation. Although we cannot exclude that effects of MR overexpression may be apparent in some of the tasks under different testing conditions, the current data suggest that MR overexpression does not substantially alter performance of female mice in these behavioral domains. This might suggest that lack in function of MRs, rather than enhanced MR function, results in clear behavioral phenotypes (Berger et al., 2006; Zhou et al., 2010; ter Horst et al., 2012, 2013).

Author Contributions

Authors have made substantial contributions to the following: Conception and design of the study: SK, HJK, MJ. Interpretation of data: SK, MSO, APH, HJK, MJ, JRS. Acquisition of data: SK, LEK, MA, HJK. Analysis of data: SK, LEK, MA. Drafting the article critically for important intellectual content: SK, MSO, APH, JRS, MJ, HJK. Final approval of the version to be submitted: SK, LEK, MA, MSO, APH, JRS, HJK, MJ. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SK, LEK, MA, MSO, APH, JRS, HJK, MJ.

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References

Akkerman, S., Blokland, A., Reneerkens, O., van Goethem, N. P., Bollen, E., Gijselaers, H. J., et al. (2012). Object recognition testing: methodological considerations on exploration and discrimination measures. *Behav. Brain Res.* 232, 335–347. doi: 10.1016/j.bbr.2012.03.022

Arp, J. M., ter Horst, J. P., Kanatsou, S., Fernández, G., Joëls, M., Krugers, H. J., et al. (2014). Mineralocorticoid receptors guide spatial and stimulus-response learning in mice. *PLoS One* 9:e86236. doi: 10.1371/journal.pone.0086236

Balderas, I., Rodriguez-Ortiz, C. J., Salgado-Tonda, P., Chavez-Hurtado, J., McGaugh, J. L., and Bermudez-Rattoni, F. (2008). The consolidation of object and context recognition memory involve different regions of the temporal lobe. *Learn. Mem.* 15, 618–624. doi: 10.3410/f.1120613.576828

Barsegyan, A., McGaugh, J. L., and Roozendaal, B. (2014). Noradrenergic activation of the basolateral amygdala modulates the consolidation of object-in-context recognition memory. *Front. Behav. Neurosci.* 8:160. doi: 10.3389/fnbeh.2014.00160

Berger, S., Wolfer, D. P., Selbach, O., Alter, H., Erdmann, G., Reichardt, H. M., et al. (2006). Loss of the limbic mineralocorticoid receptor impairs behavioral plasticity. *Proc. Natl. Acad. Sci. U S A* 103, 195–200. doi: 10.1073/pnas.0503878102

Brinks, V., Berger, S., Gass, P., de Kloet, E. R., and Oitzl, M. S. (2009). Mineralocorticoid receptors in control of emotional arousal and fear memory. *Horm. Behav.* 56, 232–238. doi: 10.1016/j.yhbeh.2009.05.003

Brinks, V., de Kloet, E. R., and Oitzl, M. S. (2008). Strain specific fear behavior and glucocorticoid response to aversive events: modeling PTSD in mice. *Prog. Brain Res.* 167, 257–261. doi: 10.1016/s0079-6123(07)67019-8

Critchlow, V., Liebelt, R. A., Bar-Sela, M., Mountcastle, W., and Lipscomb, H. S. (1963). Sex difference in resting pituitary-adrenal function in the rat. *Am. J. Physiol.* 205, 807–815.

de Kloet, E. R., Joëls, M., and Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nat. Rev. Neurosci.* 6, 463–475. doi: 10.1038/nrn1683

de Kloet, E. R., Oitzl, M. S., and Joëls, M. (1999). Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci.* 22, 422–426. doi: 10.1016/s0166-2236(99)01438-1

DeRijk, R. H., Wüst, S., Meijer, O. C., Zennaro, M. C., Federenko, I. S., Hellhammer, D. H., et al. (2006). A common polymorphism in the

mineralocorticoid receptor modulates stress responsiveness. *J. Clin. Endocrinol. Metab.* 91, 5083–5089. doi: 10.1210/jc.2006-0915

Di, S., Malcher-Lopes, R., Halmos, K. C., and Tasker, J. G. (2003). Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J. Neurosci.* 23, 4850–4857.

Dix, S. L., and Aggleton, J. P. (1999). Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition. *Behav. Brain Res.* 99, 191–200. doi: 10.1016/s0166-4328(98)00079-5

Eacott, M. J., and Norman, G. (2004). Integrated memory for object, place and context in rats: a possible model of episodic-like memory? *J. Neurosci.* 24, 1948–1953. doi: 10.1523/jneurosci.2975-03.2004

Figueiredo, H. F., Dolgas, C. M., and Herman, J. P. (2002). Stress activation of cortex and hippocampus is modulated by sex and stage of estrus. *Endocrinology* 143, 2534–2540. doi: 10.1210/en.143.7.2534

Groc, L., Choquet, D., and Chaouloff, F. (2008). The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. *Nat. Neurosci.* 11, 868–870. doi: 10.1038/nn.2150

Groeneweg, F. L., Karst, H., de Kloet, E. R., and Joëls, M. (2011). Rapid non-genomic effects of corticosteroids and their role in the central stress response. *J. Endocrinol.* 209, 153–167. doi: 10.1530/JOE-10-0472

Joels, M., and Baram, T. Z. (2009). The neuro-symphony of stress. *Nat. Rev. Neurosci.* 10, 459–466. doi: 10.1038/nrn2632

Karst, H., Berger, S., Erdmann, G., Schütz, G., and Joëls, M. (2010). Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc. Natl. Acad. Sci. U S A* 107, 14449–14454. doi: 10.1073/pnas.0914381107

Karst, H., Berger, S., Turiault, M., Tronche, F., Schütz, G., and Joëls, M. (2005). Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc. Natl. Acad. Sci. U S A* 102, 19204–19207. doi: 10.1073/pnas.0507572102

Kitay, J. I. (1961). Sex differences in adrenal cortical secretion in the rat. *Endocrinology* 68, 818–824. doi: 10.1210/endo-68-5-818

Kitraki, E., Kremmyda, O., Youlatos, D., Alexis, M., and Kittas, C. (2004). Spatial performance and corticosteroid receptor status in the 21-day restraint stress paradigm. *Ann. N. Y. Acad. Sci.* 1018, 323–327. doi: 10.1196/annals.1296.039

Klok, M. D., Alt, S. R., Irurzun Lafitte, A. J., Turner, J. D., Lakke, E. A., Huitinga, I., et al. (2011). Decreased expression of mineralocorticoid receptor mRNA and its splice variants in postmortem brain regions of patients with major depressive disorder. *J. Psychiatr. Res.* 45, 871–878. doi: 10.1016/j.jpsychires.2010.12.002

Kuningas, M., de Rijk, R. H., Westendorp, R. G., Jolles, J., Slagboom, P. E., and van Heemst, D. (2007). Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. *Neuropsychopharmacology* 32, 1295–1301. doi: 10.1038/sj.npp1301260

Lai, M., Horsburgh, K., Bae, S. E., Carter, R. N., Stenvers, D. J., Fowler, J. H., et al. (2007). Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. *Eur. J. Neurosci.* 25, 1832–1842. doi: 10.1111/j.1460-9568.2007.05427.x

Mumby, D. G., Gaskin, S., Glenn, M. J., Schramek, T. E., and Lehmann, H. (2002). Hippocampal damage and exploratory preferences in rats: memory for objects, places and contexts. *Learn. Mem.* 9, 49–57. doi: 10.1101/lm.41302

O'Brien, N., Lehmann, H., Lecluse, V., and Mumby, D. G. (2006). Enhanced context-dependency of object recognition in rats with hippocampal lesions. *Behav. Brain Res.* 170, 156–162. doi: 10.1016/j.bbr.2006.02.008

Otte, C., Wingenfeld, K., Kuehl, L. K., Kaczmarczyk, M., Richter, S., Quante, A., et al. (2015). Mineralocorticoid receptor stimulation improves cognitive function and decreases cortisol secretion in depressed patients and healthy individuals. *Neuropsychopharmacology* 40, 386–393. doi: 10.1038/npp.2014.181

Pugh, C. R., Tremblay, D., Fleshner, M., and Rudy, J. W. (1997). A selective role for corticosterone in contextual-fear conditioning. *Behav. Neurosci.* 111, 503–511. doi: 10.1037//0735-7044.111.3.503

Reul, J. M., and de Kloet, E. R. (1985). Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* 117, 2505–2511. doi: 10.1210/endo-117-6-2505

Rozeboom, A. M., Akil, H., and Seasholtz, A. F. (2007). Mineralocorticoid receptor overexpression in forebrain decreases anxiety-like behavior and alters the stress response in mice. *Proc. Natl. Acad. Sci. U S A* 104, 4688–4693. doi: 10.1073/pnas.0606067104

Schwabe, L., Schächinger, H., de Kloet, E. R., and Oitzl, M. S. (2010). Corticosteroids operate as a switch between memory systems. *J. Cogn. Neurosci.* 22, 1362–1372. doi: 10.1162/jocn.2009.21278

Schwabe, L., Tegenthoff, M., Höffken, O., and Wolf, O. T. (2013). Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. *Biol. Psychiatry* 74, 801–808. doi: 10.1016/j.biopsych.2013.06.001

Spanswick, S. C., and Dyck, R. H. (2012). Object/context specific memory deficits following medial frontal cortex damage in mice. *PLoS One* 7:e43698. doi: 10.1371/journal.pone.0043698

Spanswick, S. C., and Sutherland, R. J. (2010). Object/context-specific memory deficits associated with loss of hippocampal granule cells after adrenalectomy in rats. *Learn. Mem.* 17, 241–245. doi: 10.1101/lm.1746710

ter Horst, J. P., Kentrop, J., Arp, M., Hubens, C. J., de Kloet, E. R., and Oitzl, M. S. (2013). Spatial learning of female mice: a role of the mineralocorticoid receptor during stress and the estrous cycle. *Front. Behav. Neurosci.* 7:56. doi: 10.3389/fnbeh.2013.00056

ter Horst, J. P., van der Mark, M. H., Arp, M., Berger, S., de Kloet, E. R., and Oitzl, M. S. (2012). Stress or no stress: mineralocorticoid receptors in the forebrain regulate behavioral adaptation. *Neurobiol. Learn. Mem.* 98, 33–40. doi: 10.1016/j.nlm.2012.04.006

van Leeuwen, N., Bellingrath, S., de Kloet, E. R., Zitman, F. G., DeRijk, R. H., Kudielka, B. M., et al. (2011). Human Mineralocorticoid Receptor (MR) gene haplotypes modulate MR expression and transactivation: implication for the stress response. *Psychoneuroendocrinology* 36, 699–709. doi: 10.1016/j.psyneuen.2010.10.003

Yau, J. L., Noble, J., and Seckl, J. R. (1999). Continuous blockade of brain mineralocorticoid receptors impairs spatial learning in rats. *Neurosci. Lett.* 277, 45–48. doi: 10.1016/s0304-3940(99)00858-7

Zhou, M., Bakker, E. H., Velzing, E. H., Berger, S., Oitzl, M., Joëls, M., et al. (2010). Both mineralocorticoid and glucocorticoid receptors regulate emotional memory in mice. *Neurobiol. Learn. Mem.* 94, 530–537. doi: 10.1016/j.nlm.2010.09.005

Zhou, M., Conboy, L., Sandi, C., Joëls, M., and Krugers, H. J. (2009). Fear conditioning enhances spontaneous AMPA receptor-mediated synaptic transmission in mouse hippocampal CA1 area. *Eur. J. Neurosci.* 30, 1559–1564. doi: 10.1111/j.1460-9568.2009.06951.x

Zhou, M., Kindt, M., Joëls, M., and Krugers, H. J. (2011). Blocking mineralocorticoid receptors prior to retrieval reduces contextual fear memory in mice. *PLoS One* 6:e26220. doi: 10.1371/journal.pone.0026220

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HYPOTHESIS AND THEORY
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A neurophenomenological model for the role of the hippocampus in temporal consciousness. Evidence from confabulation

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Confabulation, the production of statements or actions that are unintentionally incongruous to the subject's history, background, present and future situation, is a rather infrequent disorder with different aetiologies and anatomical lesions. Although they may differ in many ways, confabulations show major similarities. Their content, with some minor exceptions, is plausible and therefore indistinguishable from true memories, unless one is familiar with the patient's history, background, present and future situation. They extend through the whole individuals' temporality, including their past, present and future. Accordingly, we have proposed that rather than a mere memory disorder; confabulation reflects a distortion of Temporal Consciousness (TC), i.e., a specific form of consciousness that allows individuals to locate objects and events according to their subjective temporality. Another feature that confabulators share is that, regardless of their lesion's location, they all have a relatively preserved hippocampus (Hip), at least unilaterally. In this article, we review data showing differences and similarities among forms of confabulation. We then describe a model showing that the hippocampus is crucial both for the normal functioning of TC and as the generator of confabulations, and that different types of confabulation can be traced back to a distortion of TC resulting from damage or disconnection of brain areas directly or indirectly connected to the hippocampus. We conclude by comparing our model with other models of memory and confabulation.

Keywords: memory, amnesia, confabulation, consciousness

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Introduction

Confabulation is a kind of memory distortion, that, at a general level, can be defined as the production of statements or actions that are unintentionally incongruous to the subject's history, background, present and future situation (Dalla Barba, 1993a; Dalla Barba et al., 1997b). Classically described in Korsakoff's syndrome, following lesions of the mammillary bodies and the dorsomedial nucleus of the thalamus (TH), and often present after lesions to the orbitofrontal cortex (OFC), confabulation is observed in several conditions affecting the nervous system and follows

lesions located in more than 20 anterior and posterior brain areas (Dalla Barba and Boissé, 2010).

Since the early description of this phenomenon, clinicians and scientists have distinguished between different forms of confabulation (Bonhoeffer, 1904; Berlyne, 1972; Dalla Barba, 1993a; Schnider, 2008). One of the most influential distinctions between types of confabulation is the one proposed by Kopelman (1987) between provoked and spontaneous confabulations. Like other distinctions, the one proposed by Kopelman shows advantages and limits. The advantage is that it provides a separation between phenomena that may reflect differing underlying cognitive and neural mechanisms. The limit is that it fails to classify a number of confabulations that are not appropriately captured by either of the distinction's terms. It has been proposed and used elsewhere a new taxonomy of confabulation, showing that, regardless their modality of appearance, provoked *vs.* spontaneous, confabulations are plausible memories, mainly reflecting the recall of repeated personal events mistakenly considered by the confabulating patient as specific and unique events that occurred in a specific and unique temporo-spatial context. This, by far the more frequent type of confabulation, was named "Habits Confabulation" (Dalla Barba and Boissé, 2010; La Corte et al., 2010) and it was traced back to the disruption of the cognitive mechanism that allows individuals to discriminate between "uniqueness", i.e., specific unique events, and "multiplicity", i.e., repeated events, habits and routines (Serra et al., 2014). In these studies, "bizarre", "implausible", "fantastic" confabulations, either spontaneous or provoked represented less than 5% of the total number of confabulations.

Although they may differ in many ways, confabulations show major similarities:

1. Their content, with some minor exceptions, is plausible and therefore indistinguishable from true memories, unless one knows the patient's past, present and probable future situation (Dalla Barba, 1993a).
2. They extend through the whole individuals' temporality, including their past, episodic memory, their orientation in their present world and their ability to predict their personal future (Dalla Barba et al., 1990, 1997b, 1999; Dalla Barba, 1993a; Nedjam et al., 2000; Schnider, 2008; La Corte et al., 2010). Accordingly, Dalla Barba (2002) proposed that rather than a mere memory disorder, confabulation reflects a distortion of Temporal Consciousness (TC), i.e., a specific form of consciousness that allows individuals to have phenomenological experience of remembering their personal past, of being oriented in their present world and of predicting their personal future.
3. It is uncontroversial that patients with documented, complete, bilateral hippocampal damage are amnesics, but don't confabulate, whereas, regardless of their lesion's location, confabulators all have a relatively preserved hippocampus, at least unilaterally (Gilboa and Moscovitch, 2002; Dalla Barba and Boissé, 2010).

Accordingly, Dalla Barba and La Corte (2013) proposed a model in which the hippocampus is the neural correlate of TC, which is lost in hippocampal amnesia and malfunctioning in confabulation.

According to the model they proposed, lesions occurring to brain areas and pathways upstream or downstream an intact or partially preserved hippocampus produce different types and possibly different modality of appearance of confabulation. In that model the hippocampus plays a passive role receiving directly from upstream pathways, or indirectly, through the cingulum and the retrosplenial cortex already distorted information. The aim of the present work is to further develop the previous model. In this new perspective, a partially damaged hippocampus may still allow TC to exist, but may loose its peculiarity of segregating and organizing information in the temporo-parietal cortex (TPC).

In this article, we review data showing differences and similarities among forms of confabulation. We then develop the model sketched in our previous work (Dalla Barba and La Corte, 2013) showing that the hippocampus is crucial both for the normal functioning of TC and as the generator of confabulations, and that different types of confabulation can be traced back to a distortion of TC resulting from damage or disconnection of brain areas directly or indirectly connected to the hippocampus.

The model described in this work is a "neuro-phenomenological" one, in the sense that it combines the phenomenological description of confabulation and neurological or neurocognitive experimental accounts of the issues treated in this work.

Varieties of Confabulation: Differences and Similarities

Differences in Etiology and Anatomy

Confabulation is a rather infrequent disorder with different aetiologies and anatomical lesions. It is a pathognomonic sign of Korsakoff's syndrome (Korsakoff, 1889; Bonhoeffer, 1904; Wyke and Warrington, 1960; Talland, 1961; Mercer et al., 1977; Cermak et al., 1980; Dalla Barba et al., 1990; Benson et al., 1996; Schnider et al., 1996a), but is observed also in other pathological conditions, namely in patients suffering from ruptured aneurism of the anterior communicating artery, subarachnoid haemorrhage or encephalitis (Luria, 1976; Stuss et al., 1978; Kapur and Coughlan, 1980; Alexander and Freedman, 1984; Moscovitch, 1989, 1995; Delbecq-Derouesné et al., 1990; DeLuca and Cicerone, 1991; Irle et al., 1992; Kopelman et al., 1995; Papagno and Muggia, 1996; Schnider et al., 1996b; Dalla Barba et al., 1997b; Diamond et al., 1997), head injury (Weinstein and Lyerly, 1968; Baddeley and Wilson, 1986; Dalla Barba, 1993b), Binswanger's Encephalopathy (Dalla Barba, 1993a), Alzheimer's disease (AD) and frontotemporal dementia (Kern et al., 1992; Dalla Barba et al., 1999; Nedjam et al., 2000, 2004; Attali et al., 2009) and aphasia (Sandson et al., 1986). On occasion, or in particular experimental conditions, confabulation may also be observed in normal subjects (Kopelman, 1987; Burgess and Shallice, 1996b; Dalla Barba et al., 2002).

At a general level, distinctions between types of confabulation are considered to reflect different underlying brain lesions. Anterior brain lesions, in particular in the OFC basal forebrain

and related structures, have been consistently associated with spontaneous confabulations (Kopelman, 1987; Moscovitch, 1995; Schnider et al., 1996a; Schnider and Ptak, 1999; Gilboa et al., 2006b). Spontaneous confabulations, however, can also occur with lesions not involving the OFC and related structures (Dalla Barba, 1993a; Dalla Barba and Boissé, 2010; La Corte et al., 2011). Other types of confabulation lack a specific anatomical basis, but are usually related to posterior cortical and subcortical lesions sparing the OFC and related structures. Overall, lesions in more than 20 brain regions have been reported in confabulation (Gabrieli et al., 1988; Gilboa and Moscovitch, 2002; Dalla Barba and Boissé, 2010). Therefore, unlike many other neuropsychogical disorders, e.g., aphasic syndromes, confabulation is not associated with a specific lesion site.

Similarities in Content

Regardless of their etiology and anatomy, most confabulations are indistinguishable from true memories, in the sense that their content is plausible, mostly consisting of habits, repeated events or over-learned information mistakenly considered as specific unique episodes, so that an observer blind to the patient's past, present and future situation wouldn't be able to tell whether the patient is confabulating or not (Dalla Barba, 1993a; Dalla Barba et al., 1997b, 1999; Burgess and McNeil, 1999; La Corte et al., 2010). The case of patient MG (Dalla Barba et al., 1997a) well illustrates how confabulations can go undetected when the real present and past situation of a patient is unknown. While he was waiting to undergo a CT scan, MG told the radiologist that he had accompanied a friend to be admitted to the neurology department that day. The neurologist who was taking care of MG's (inexistent) friend realized that MG also had neurological problems and so decided to refer him to the radiology department for a CT scan. On that occasion the radiologist did not even suspect that MG was confabulating. Another example is the following:

– How did your disease begin? Asks the doctor to patient CA.
– It started with a strong sore throat . . . I couldn't swallow anything . . . so I couldn't go to school . . . my mother called the doctor, answers the patient.
– How did your disease begin? Asks the same doctor to another patient, CD.
– It started with a strong headache . . . one morning I woke up with a strong headache and then I started throwing up and I remember I couldn't keep my eyes open, answers the patient.

One of these two patients is confabulating, whereas the other one is reporting the memory of an event she has really experienced. As you can see, there is nothing in the patients' reports that can help you to tell which patient is confabulating. However, if we tell you that CA is a 67-year-old woman with Korsakoff's syndrome (Dalla Barba et al., 1990) and that CD is a 33-year-old woman reporting the onset of her Herpes meningitis, things become much more clear and these additional pieces of information allow you to identify CA as the confabulating patient. This is not because you know that patients with Korsakoff's syndrome confabulate, but rather because you know that it is quite unlikely that somebody who is 67-year-old goes to school and has a mother who calls the doctor for her sore throat. In addition you know that headache, vomiting and photophobia are common in the onset of Herpes meningitis, which suggests you that CD is not confabulating. Nevertheless, CA's and CD's reports have something in common. They are plausible (Dalla Barba, 1993a) in the sense that an observer blind to the patient's personal past wouldn't be able to tell whether the patient is confabulating or not.

Temporal Similarities

However, the confabulators' tendency to mistake habits and repeated events as unique episodes encompasses not only their personal past, but involves their personal present and future as well. In fact, they often confabulate about their present situation (Dalla Barba et al., 1990, 1998; Dalla Barba, 1993a; Burgess and McNeil, 1999; La Corte et al., 2010, 2011) saying, for example, that they are at school rather than at the hospital (Dalla Barba et al., 1990), and make confabulating errors concerning their personal future, saying, for example, that the following day they will be going at work, although they are not working anymore (Burgess and McNeil, 1999; Schnider, 2008; La Corte et al., 2011). Sometimes they also act upon their confabulated present and future. Patient MB (Dalla Barba, 1993a), for example, on one occasion said that he was looking forward to the end of the testing session because he had to go to the general store to buy some new clothes, since he hadn't been able to the day before. On this occasion the patient actually attempted to leave his hospital room, claiming that there was a taxi waiting for him downstairs. The patient's tendency to confabulate in the three dimensions of personal temporality—past, present and future—has been consistently reported using the Confabulation Battery (Dalla Barba, 1993a; Dalla Barba and Decaix, 2009) in 20 patients with confabulatory syndromes of various aetiologies and with different brain lesions (Dalla Barba et al., 1997a,b; Dalla Barba and Boissé, 2010; La Corte et al., 2010, 2011).

Anatomical Similarities

Regardless the lesions' heterogeneity, confabulators have at least partial preservation of the hippocampus (used here to refer to the hippocampus proper together with the dentate gyrus and the subicular cortex). In a review of 79 cases of confabulation, it was found that none of these patients had hippocampal lesions (Gilboa and Moscovitch, 2002). Other 28 confabulators, not considered in the above review, also had normal hippocampi (Dalla Barba et al., 1990, 1997b; Dalla Barba, 1993a; Fotopoulou et al., 2004, 2007; Ciaramelli et al., 2006; Ciaramelli and Ghetti, 2007). Damage to the hippocampus has long been known to produce amnesia (Scoville and Milner, 1957), i.e., a retrograde and anterograde episodic memory deficit "out of all proportion to other memory and cognitive functions in an otherwise alert and responsive patient" (Victor et al., 1971). Episodic memory dysfunction varies according to the degree of hippocampal damage. In early AD, mild to moderate hippocampal atrophy

induces mild to moderate episodic memory deficit. Episodic memory is completely abolished following complete, bilateral hippocampal damage. Amnesic patients show normal or close to normal performance on a number of implicit learning and memory tasks, have preserved linguistic skills and have relatively preserved general knowledge or semantic memory. In contrast, they are completely unable to learn and retain any new information, show extensive retrograde amnesia, and have no phenomenological experience of remembering their personal past and of predicting their personal future. In these patients, who are sometime described as stucked in an instantaneous present, the three dimensions of personal temporality, past, present and future, are lost. They have no difficulties with physical or chronological time (Husserl, 1893). They have preserved semantic knowledge of units of time and their relationships (Tulving, 1985). They have relatively preserved knowledge of past public and historical events and they can predict episodes and events in the public domain (Klein et al., 2002). But in contrast with this preserved knowledge of physical and impersonal time, their awareness of subjective time is severely impaired. Accordingly, classic hippocampal amnesia cannot be considered a pure episodic memory deficit, but rather a pathological condition affecting individuals' episodic subjective temporality.

Within the framework of the Memory, Consciousness and Temporality Theory (MCTT; Dalla Barba, 2002), it has been proposed that confabulation reflects a distortion of TC, whereas classic amnesia due to hippocampal damage reflects a loss of TC.

The Memory, Consciousness and Temporality Theory (MCTT)

In line with the continental phenomenological tradition (Brentano, 1874; Sartre, 1943; Merleau-Ponty, 1945; Husserl, 1950), the MCTT considers that consciousness is not an aspecific entity, but is intentionally projected toward its object, being always consciousness of *something*. Here and hereafter the object of consciousness is not meant to be necessarily a physical object, but it is what consciousness is addressing, a physical object, e.g., a pen, or an abstract object, e.g., an event. Consciousness addresses its object in different ways, implying that different types, or modes of consciousness exist. For example, this pen in front of me on the desk, I can perceive it, if I close my eyes, I can imagine it, I can hate it or like it, I can know it, e.g., know that is it is a pen and not a sailing boat, I can remember it, e.g., remember where and when I bought it. All these different relationships between consciousness and its object are *original*, because each one differs from each other and *irreducible*, because they are not the final result of a causal or ontological cascade. The aim of this work is not to detail a taxonomy of different types of consciousness, but to use the distinction made by Dalla Barba (2002) between TC and Knowing Consciousness (KC).

KC is defined as a specific form of consciousness allowing individuals to be aware of past, present and future *impersonal* knowledge and information. KC concerns, for example, knowing that G. W. Bush was the past President of the United States, that Obama is currently in charge of that position and that in the next Presidential elections he will be not allowed to run for a third term. KC is usually relatively preserved in both confabulating and non confabulating amnesics (Dalla Barba et al., 1997b; Klein et al., 2002; Dalla Barba and Boissé, 2010; La Corte et al., 2010, 2011). Patients who have no phenomenological experience of remembering their personal past and of predicting their personal future not only are able to retrieve impersonal past information, i.e., semantic memories, but are also able to predict the impersonal future. For example, they have no difficulties in answering questions like "What is likely to be an important breakthrough in the medical domain in the next 10 years?" (Klein et al., 2002; La Corte et al., 2010, 2011). They also have preserved "personal semantics", i.e., they have access to personal past and present factual information. They can correctly give, for example their date of birth and they can tell that they went to school and then graduated. They can also use this information to make inferences about their future. Yet none of these cases do they have the phenomenological experience of remembering specific episodes from their personal past and of predicting specific episodes in their personal future.

TC is a specific form of consciousness that allows individuals to have phenomenological experience of remembering their personal past, of being oriented in their present world and of predicting their personal future (Dalla Barba and La Corte, 2013). It is this type of consciousness that defines individuals as temporal entities with a personal past, present and future. Personal temporality, as expressed by TC, is different from impersonal temporality, as expressed by KC. Patients without TC, due to bilateral hippocampal damage (see below) still have impersonal temporality, i.e., they can access and use impersonal past, present and future information, but they have lost the personal dimension of time. They can learn and *know* things about their past, as they can *know* things about their future. They can even learn their entire biography (see below the description of patient RM), but they have no phenomenological experience of remembering their past and of projecting themselves in specific future situations.

In normal conditions, TC addresses the object's *Uniqueness* (U), whereas KC addresses the object' *Multiplicity* (M). Let's consider the following example. This pen on the desk reveals both an U and a M, according to how my consciousness address it. It represents a U if I consider it *that-specific-pen-I-bought-last-week-and-that-I-will-be-using-this-afternoon-to-sign-a-cheque*. It represents a M if I consider it *an-indeterminate-pen-belonging-to-the-category-of-pens*. In short, U means *this specific pen* and not another one, whereas M means *a pen*, an object belonging to the multiplicity of objects of the same category. Accordingly to how consciousness addresses its object, the pen in this example, the object reveals a U, or a M. Anticipating what will be discussed later on, in normal conditions, TC's object represents U, whereas KC's object represents M.

In the next section, we will see how what we have discussed so far is relevant to the interpretation of confabulation.

Temporal Consciousness, Confabulation and Amnesia

In confabulators, TC is present, but it is malfunctioning, because these patients confabulate when questioned about their past, present and future. Conversely, non-confabulating amnesics, who have lost TC, have no phenomenological experience of remembering their personal past and of predicting their personal future. An increasing number of studies have addressed the question of the neurocognitive relationship between episodic memory and the individuals' ability to predict their personal future. What is referred to, as memory of the future (Ingvar, 1985), planning (Dalla Barba et al., 1997b) or imagining the future (Klein et al., 2002; Schacter et al., 2007), mental time travel (Suddendorf and Corballis, 2007) and chronesthesia (Tulving, 2002) are aspects of TC as described in the MCTT (Dalla Barba, 2002). Schacter et al. (2007) propose that remembering the past is necessary to imagine the future. However, although remembering the past and imagine the future depend much on the same neural machinery, namely the medial temporal lobe, there is no ontological priority of remembering vs. predicting the future. In other words remembering is not a prerequisite to predict the future. It is not because I remember that I had a cup of thee this morning that I am able to predict having sushi for dinner tonight.

As reported elsewhere by Dalla Barba and co-workers (Dalla Barba and Boissé, 2010; Dalla Barba and La Corte, 2013), aspects of the MCTT relevant to the interpretation of confabulation and amnesia are summarized below.

1. Events produce atemporal and aspecific patterns of modifications in the brain. These modifications, are atemporal in the sense that they do not contain any information concerning time. They do not represent the past, the present or the future, nor are they organized according to the order of succession, i.e., there is nothing in Y, for example, that tells that Y come before Z and after X. They are aspecific in the sense that they do not contain any information specifying that they are representing episodes, meanings, rules, procedures, or algorithms.
2. The patterns of modifications in the brain can be more or less stable and more or less vulnerable depending on a number of variables. These variables include, among others, attention at encoding, emotional value of the event, depth of encoding, rehearsal and repeated experience of the same or of a similar event.
3. TC is a specific form of consciousness that allows individuals to have phenomenological experience of remembering their personal past, of being oriented in their present world and of predicting their personal future. It is specific because it cannot be confounded with other forms of consciousness, such as, for example, perception and imagination. If, for instance, the average person perceives a tiger in front of them, they will be scared, but if they remember or imagine such an event, they may not be scared at all.
4. TC is experimentally measurable and dissociable from impersonal temporality. Using the Confabulation Battery, which includes 11 dependent variables (Dalla Barba, 1993a; Dalla Barba and Decaix, 2009), it has been demonstrated that confabulators and amnesics either confabulate or have no phenomenological experience of remembering their personal past and of predicting their personal future, whereas they are able to answer questions about impersonal past, present, and future (e.g., what happened to Princess Diana, who the President of the United States is and what is likely to be one of the most important breakthrough in the medical domain in the next 10 years; La Corte et al., 2011; Klein et al., 2002).
5. TC is lost in amnesia following complete bilateral hippocampal damage and malfunctioning in confabulation, because it receives distorted information from more than 20 damaged, predominantly orbitofrontal, brain areas.
6. The object of consciousness represents a determination and an indeterminateness, what we have called U and M. U refers to unique events, whereas M refers to repeated events. TC addresses the object's U, whereas KC addresses its M.

In normal conditions, TC interacts with less stable patterns of modification of the brain in order to seize the object's U, past, present or future, whereas KC, interacts with more stable patterns of modification of the brain in order to seize the object's M. The interaction between TC and less stable patterns of modification of the brain allows individuals to identify the "pen" as a U, i.e., as an object belonging to a personal temporality—I have used this pen yesterday to sign a cheque, it is now in front of me, just some inches beside the computer's keyboard, and I can predict using it tomorrow to sign another cheque for the plumber. In contrast, the interaction of KC with more stable patterns of modification of the brain allows people to identify the "pen" as a M, i.e., as a specific object, which is different from other objects—this pen in front of me is different from the computer's keyboard, although they share similar functions.

In amnesia TC is lost. Non-confabulating amnesic patients don't have any phenomenological experience of remembering or of predicting specific unique events in their personal past or personal future. They can recognize elements of their life as familiar, but this, in the framework of the present theory, does not reflect uniqueness. They can say: "this is my dog, my mother, my car, my house", but they don't have any phenomenological experience of remembering or of predicting any specific unique episode concerning their dog, mother, car or house. In other words, since they have lost TC, they have lost the possibility of segregating specific episodic information within a network of information, which is the necessary condition to access objects' uniqueness (see below).

In confabulation, TC is still present, but it is not interacting with less stable patterns of modification of the brain, because these modifications are abolished or inaccessible in the mode of TC. In this condition, TC interacts with more stable patterns of modifications of the brain, and the result is that repeated events, habits and over-learned informations, in short the object's multiplicity, are seized as unique events, past, present or future. It is clinically well known, for instance, that hospitalized confabulators, when directly questioned on what they have done the previous day, usually report routine activities from their

life before the accident. For example, they may say that the previous day they went to work or that they had dinner at home "as usual". In this case, irretrievable episodic memories, i.e., events that occurred in a unique and specific temporo-spatial context, are replaced by routines, i.e., multiple, repeated events that didn't occur in a unique and specific temporo-spatial context. Therefore we can say that M, i.e., routines and repeated events, is mistaken for U, i.e., a specific unique event that occurred in a specific, unique temporo-spatial context (such as the previous day). This clinically well known observation has been experimentally demonstrated for the first time in a recent work from the Dalla Barba's group (Serra et al., 2014). In order to measure the ability to discriminate unique from repeated events the authors used four runs of a recognition memory task, in which some items were seen only once at study, whereas others were seen four times. Confabulators, but not non-confabulating amnesics, considered repeated items as unique, thus mistaking M for U. The authors suggested that a crucial mechanism involved in the production of confabulations is thus the confusion between unique and repeated events.

It might be argued that this account may explain Habits Confabulations, but not other types of plausible confabulations, which do not necessarily arise from the patient's own life. The example of patient MG and the radiologist described earlier in this paper reports a plausible confabulation, but there is no evidence that the patient ever went visiting a friend admitted to a neurology department. However, Habits Confabulations, the most common form, and other types of plausible confabulation may rely on very similar mechanisms involving the hippocampus ability to segregate and organize information in the temporo-parietal associative cortex. In the Dalla Barba and La Corte (2013) model the hippocampus played a sort of "passive" role. It passively received distorted information directly from the TPC or indirectly, through the cingulum, and "temporalized" them in a personal temporal framework. The result of this condition is that the hippocampus produces confabulation because it receives distorted information from upstream or downstream from other brain areas it is connected with. In the Dalla Barba and La Corte (2013) model, the hippocampus is a brain structure that receives distorted information and locates them in a personal temporal framework. However, it is known and accepted (e.g., Hardt et al., 2013) that the hippocampus has also an active role. It acts as a sort of "pointer", making a fine-grained search in the neocortex segregating specific episodic information within a network of information, which is not (necessarily) pertinent to the goal, i.e., the retrieval of specific episodic memories. If the hippocampus is partially damaged, it may select plausible information based on the patient's habits. However, if plausible habits are unavailable, or do not fit the current demands, it may make an "abductive inference" (Coltheart et al., 2010), providing the best plausible explanation of the patient's current situation.

In the La Corte et al. (2010) study "bizarre", "implausible", "fantastic", "semantically anomalous" confabulations, either spontaneous or provoked represented less than 5% of the total number of confabulations. The model proposed here accounts for this type of confabulation. Lesions upstream the hippocampus may produce deep semantic deficits, which may produce "semantically anomalous" confabulation (Dalla Barba, 1993b), i.e., confabulations with semantically incoherent content. Lesions downstream the hippocampus, in particular in the OFC may produce "fantastic" or "bizarre" confabulations. It is well known that patients with orbitofrontal lesions often show inadequate and bizarre behavior. This type of behavior may extend to the memory domain and to the domain of TC in general.

In contrast to confabulation, in amnesia, due to complete hippocampal damage, TC is lost. Patients with classical amnesia are unable to temporalize objects. They can't remember their past, they are disoriented in the present world and they are unable to prospect their future. Since in these patients TC is lost, no interaction is possible between TC and more or less stable patterns of modification of the brain. In contrast, in these patients, KC is relatively preserved and interacts normally with more stable patterns of modification of the brain. Therefore they can access and use impersonal information concerning the past, the present and the future. They can say, for example, that Kennedy was killed, that France is a republic, whereas UK is a kingdom, and that the candidate for the Democrats in the next US Presidential elections will not be Barack Obama.

Neural Correlates of Temporal Consciousness

So far we have seen that what distinguishes confabulators from non-confabulating amnesics is a distorted TC, in the first, and a loss of TC, in the latter. We have also seen that available data indicate that the integrity, at least partial or unilateral, of the hippocampus seems to be a necessary condition in order for individuals to confabulate, whereas its complete damage not only is not associated with confabulation, but results in a loss of TC, and consequently in deep amnesia.

It is known that some patients with bilateral lesions in the hippocampus confabulate. Patients with limbic encephalitis (Kikuchi et al., 1999; Nahum et al., 2010; Kartsounis and de Silva, 2011) and Pick's disease with hippocampal involvement (Kremen et al., 2010), for example, confabulate. But limbic encephalitis and Pick's disease don't lead to complete, bilateral hippocampal destruction. In the Nahum et al. (2010) study, inflammation was pronounced in the left hippocampus, but was only mild in the right one. In the Kremen et al. (2010) study, it is clearly stated that the hippocampus was relatively spared bilaterally. One case is reported to have complete limbic lobe destruction and confabulation (Gascon and Gilles, 1973). However, in this patient complete, bilateral hippocampal damage is not documented. Overall, there is overwhelming evidence supporting the conclusion that at least partially preserved hippocampus is a necessary condition for confabulation.

At variance with patients with hippocampal amnesia, patients with diencephalic amnesia have distorted TC, as defined in this and previous work from Dalla Barba and co-workers. Confabulation, which is the hallmark of a distorted TC, is a pathognomonic sign of Korsakoff's syndrome (Korsakoff, 1889; Bonhoeffer, 1904; Wyke and Warrington, 1960; Talland, 1961;

Mercer et al., 1977; Cermak et al., 1980; Dalla Barba et al., 1990; Benson et al., 1996; Schnider et al., 1996a; Borsutzky et al., 2008), which is a diencephalic amnesia. Patients with non-Korsakoff thalamic lesions (e.g., Gentilini et al., 1987; Hodges and McCarthy, 1993; Markowitsch et al., 1993; Markowitsch, 2008) and patients with orbitofrontal lesions (e.g., Kopelman, 1987; Knight et al., 1995; Moscovitch, 1995; Schnider et al., 1996a; Dalla Barba et al., 1997b; Schnider and Ptak, 1999; Gilboa et al., 2006b) show deep anterograde, more variably, retrograde amnesia and, invariably, various types of memory distortions, i.e., distorted TC, including confabulations.

Taken together, these observations show that hippocampal amnesia, complete bilateral destruction of the hippocampus, produces negative signs and symptoms, i.e., the failure to retrieve the desired information in TC, whereas non-hippocampal amnesia, diencephalic and frontal, produce positive signs such as memory distortions. This strongly suggests that the hippocampus is the neural correlate of TC (Dalla Barba and La Corte, 2013) and is supported by an increasing number of recent neuropsychological (Klein et al., 2002; Hassabis et al., 2007; Rosenbaum et al., 2007; Kwan et al., 2010) and neuroimaging (Martin, 2001; Schacter and Addis, 2007; Botzung et al., 2008; Addis et al., 2011) studies confirming that the hippocampus is a core structure within a network involved in individuals' temporal existence, i.e., their having phenomenological experience of a personal past, present and future.

Hippocampal anatomy, physiology and connectivity are all suggestive of a crucial function of this neural structure in associating experienced events in order to remember specific episodes from one's own past and to adapt to ongoing and future reality (Henke, 2010). The hippocampus is reciprocally connected, either directly or indirectly, with all neocortical association areas. It receives upstream, through the parahippocampal, perirhinal, and entorhinal cortices, projections from unimodal and polymodal neocortical association areas and projects downstream, through the fornix, to the hypothalamus, the anterior thalamus, the anterior cingulate gyrus and the OFC. Lesions to the fornix result in amnesia without confabulation, whereas confabulation has been described for lesions involving all the above neural structures, but sparing the hippocampus.

If the hippocampus is the neural correlate of TC, then its function is to *temporalize* information. This doesn't mean that the hippocampus has a subjective intentional life, like monitoring theories assume for the, anthropomorphised, frontal lobe (see Dalla Barba, 2002 for a discussion of the *homunculus* fallacy and the anthropomorphisation of the brain), but that information, normal or distorted, assumes a personal, temporal dimension when processed by the hippocampus. In normal conditions, the hippocampus accomplishes its function very well, being able to capture the events' uniqueness—that specific walk I had yesterday afternoon along the Bastille Canal and not the walk I take each day there, or the conference I will give tomorrow at 5 pm and not a general talk I will be giving in the future. It is now well known that the hippocampus is crucial for rapid, single-trial learning of flexibly integrated what-where-when information (Henke, 2010). Consistently, it has been shown that long-term potentiation following a single train of high-frequency tetanic stimulation can be induced in the hippocampus (Trepel and Racine, 1998). Thus, the normal function of the hippocampus is to temporalize unique phenomenological experiences. This function is the result of the interaction between the hippocampus and less stable patterns of modification in neocortical unimodal and polymodal association areas.

As we have seen, in keeping with some aspects of the MCTT, these patterns of modification of the neocortical association areas are atemporal and aspecific. They are atemporal because they do not represent the past, the present or the future. They are aspecific because they do not contain any information specifying that they are representing episodes, meanings, rules, procedures, or algorithms. These patterns of modifications of the neocortical areas are made temporal and specific by the hippocampus, which processes them as temporal and specific. The patterns of modification that events produce in the neocortical areas can be expressed in behavior atemporally and aspecifically, like, for example, in priming effects. In priming effect, single, unique past events influence current performance and behavior without being temporalized, i.e., they are not expressed as elements of a personal past, present or future. This is known since the pioneering clinical reports by Korsakoff, Claparède and others.

So, at present, the hippocampus is the best candidate as the neural correlate of TC, although it is involved in other functions, like reaction to novelty, single trial learning and "unconscious" episodic memory (Henke, 2010).

Hippocampus Confabulation and Amnesia

In its classical form, confabulation is observed for lesions in the mammillary bodies and the dorsomedial thalamic nucleus. It is well known that confabulation is frequently observed following lesions in the OFC and basal forebrain. These uncontroversial observations lead researchers to consider lesions to these neural structures as crucial for confabulation to occur. However, as mentioned above, confabulations are observed for lesions in more than 20 anterior and posterior cortical and subcortical areas, which are all directly or indirectly connected to the medial temporal lobe and to the hippocampus. The OFC is one of these structures to which the hippocampus projects through the fornix, mammillary bodies and TH. Lesions to the mammillary bodies and the TH, but also to the basal forebrain produce confabulations (Schnider, 2008). In short, with the exception of lesions involving the fornix, damage at any point of the pathways running downstream the hippocampus produce confabulation, provided that the hippocampus is, at least partially, preserved. If the hippocampus is severely damaged bilaterally the result is deep amnesia without confabulation (Dalla Barba and La Corte, 2013).

Brain damage involving areas projecting from upstream to a preserved hippocampus are also known to produce confabulation (Dalla Barba, 1993a,b; De Anna et al., 2008; Attali et al., 2009). As stated elsewhere (Dalla Barba and La Corte, 2013), lesions to temporoparietal association areas, or to their projections to the hippocampus, may produce confabulated memories and plans, which may differ in

content from confabulations observed from lesions involving the OFC, or structures and pathways downstream of the hippocampus. Lesions downstream of the hippocampus produce semantically appropriate confabulations, either provoked or spontaneous. Lesions upstream of the hippocampal circuit produce more implausible and semantically anomalous confabulations. Therefore, the hippocampus is likely to be the core temporal device that temporalizes personal phenomenological experiences, provided either directly by temporoparietal association areas, or, indirectly, through the Papez's circuit, by diencephalic, basal forebrain and orbitofrontal structures. Lesions upstream or downstream sparing the hippocampus may all produce confabulation. This model is presented in **Figure 1**.

Figure 1A depicts the normal functioning of the circuit. **Figure 1B** shows a complete bilateral damage to the medial temporal lobe and the hippocampus with the consequent loss of TC resulting in deep amnesia. **Figure 1C** describes lesions to temporo parietal areas or their disconnection to the hippocampus, resulting in semantically anomalous confabulations. **Figure 1D** shows lesions downstream of the hippocampal circuit producing the most common form of confabulation, which are mainly plausible, semantically coherent and indistinguishable from true memories, unless one is aware of the patient's past, present and future situation.

The anatomical basis of confabulation has been a puzzling issue. Confabulation was originally described in alcoholic patients (Korsakoff, 1889), later shown to have diencephalic lesions (Victor et al., 1971), but were then observed in patients with chronic infections, traumatic brain lesions, subarachnoid hemorrhage, brain tumors and other pathologies (for a review, see Schnider, 2008). Overall, more than 20 anterior and posterior brain lesion loci have been associated with confabulation (Gilboa et al., 2006a,b; Dalla Barba and Boissé, 2010). Confabulations are also a common finding in diffuse brain pathologies like AD and frontotemporal dementia. Therefore, it seems uncontroversial that confabulation lacks a specific neurobiological correlate, either in terms of pathology, or in terms of lesion's location. Here, we propose that the neural correlate of confabulation is the, at least partial, integrity of the hippocampus in association with lesions in brain areas that project, directly or indirectly to the hippocampus. Lesions upstream or downstream of the hippocampus may produce different types of confabulation through the disruption of different cognitive processes, but at least a partial integrity of the hippocampus is the necessary condition for confabulation to occur.

As far as the involvement in confabulation of specific regions within the hippocampus is concerned, at present no reliable data are available and consequently, no conclusion is possible. However, it is reasonable to think that CA3 and the posterior hippocampus may be crucial for the normal functioning of TC. Neuroimaging data in normal subjects as well as animal studies show that various long-axis specialisations arise out of differences between the anterior and posterior hippocampus (Poppenk et al., 2013). The anterior hippocampus is involved in coarse, global representations, whereas the posterior hippocampus is involved in fine-grained local representations. CA3 is known to be involved in pattern separation and pattern completion (Rolls, 2013; Deuker et al., 2014). Furthermore, CA3, compared to entorhinal cortex (EC), subiculum, CA1-CA2, is relatively preserved in early AD (Mueller et al., 2007, 2010), a condition in which confabulations are present (Dalla Barba et al., 1999; De Anna et al., 2008; Attali et al., 2009). Fine-grained local representations, pattern separation and pattern completion are processes possibly involved in TC's recognition of uniqueness (see above). If these processes are disrupted, then multiplicity may be mistaken for uniqueness, because interfering, distorted information from other damaged brain areas or other hippocampal subfields prevents the normal functioning of the posterior hippocampus and CA3, and consequently, of TC. Further research evaluating the role of specific hippocampal subfields in confabulation will provide possible support to what, at present, is mere speculation.

Comparison with other Models of Memory and Confabulation and Guidelines to the Falsification of the Model

TC, as used here and in other works from the Dalla Barba's group, is distinct from other types of consciousness, namely KC, Imaginative Consciousness and Perceiving Consciousness (Dalla Barba, 2002). TC is the synthesis of a set of theoretical assumptions, have some specific characteristics and is one of the core concepts of the MCTT (Dalla Barba, 2002). To summarize, TC is:

- the prediction of a concrete personal phenomenon, i.e., individuals' ability to consciously remember their past, to be consciously oriented in their present world and to consciously predict their personal future;
- experimentally measurable: questions like "Do you remember what you had for dinner last night, the last time you went to the restaurant, the last time you went for a swim?", or "Can you predict when you will be going to the restaurant, for a swim next time?" are measures of TC. The possibility to answer these questions relies on the integrity of TC, and amnesics typically either answer "I don't know" or confabulate to these questions.
- neurobiologically grounded in a specific neural structure, the hippocampus;
- lost in hippocampal amnesia and malfunctioning in confabulation, because it receives distorted information from more than 20 damaged, predominantly orbitofrontal areas.

Some authors have used the term TC in a loose and unspecified sense, not referring to what TC is in Dalla Barba' formulation. This caused to some misunderstanding. In a recent work, for example, Craver et al. (2014, p. 192) argued that La Corte et al. (2011) and Dalla Barba and La Corte's (2013) concept of TC is ambiguous, because in their definition TC "comprises many cognitive faculties, including many that are preserved in people with severe deficit in episodic memory and future thought." TC definition was probably not sufficiently clear in Dalla Barba and La Corte (2013). In the MCTT

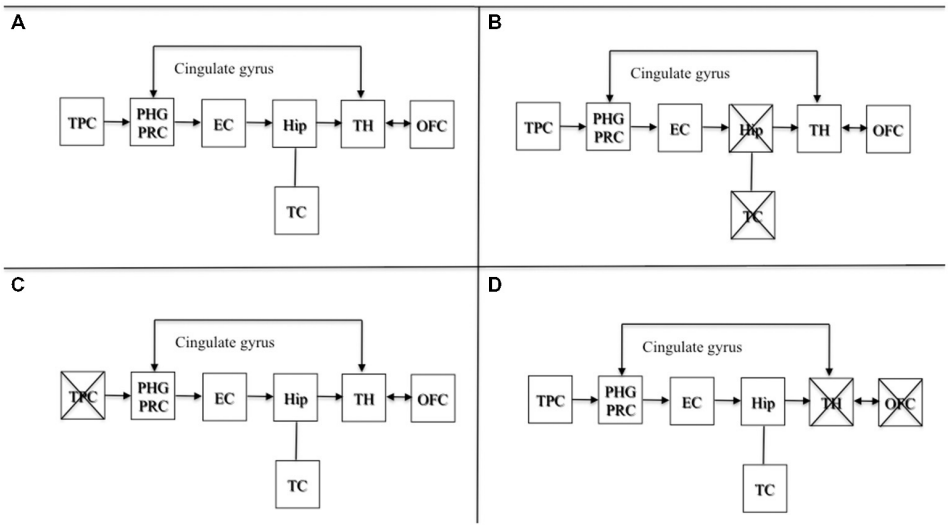


FIGURE 1 | Adapted with permission from Dalla Barba and La Corte (2013). A schematic cognitive and neuroanatomical model of normal and pathological functioning of memory and Temporal Consciousness (TC). **(A)** Normal functioning of memory and TC: the hippocampus, which is the neural correlate of TC, temporalizes information received directly from the TPC, or indirectly from the OFC and the TH, through the cingulate gyrus, allowing individuals to remember their personal past, to be oriented in their present and to predict their personal future. **(B)** Amnesia: complete, bilateral lesions to the hippocampus abolish TC, preventing individuals from accessing their personal temporality (i.e., their past, present, and future). **(C)** Implausible or semantically anomalous confabulation: lesions to the TPC provide the hippocampus with distorted semantic information, inducing the hippocampus and TC to make semantically anomalous confabulatory errors concerning the individual's personal temporality. **(D)** Plausible, or semantically appropriate confabulation: lesions to the TH and the OFC provide the hippocampus with plausible but erroneous information, inducing the hippocampus and TC to make plausible confabulatory errors concerning the individuals' personal temporality. Abbreviations: TPC, temporo-parietal cortex; PHG, parahippocampal gyrus; PRC, perirhinal cortex; EC, entorhinal cortex; Hip, hippocampus; TH, thalamus; OFC, orbitofrontal cortex; TC: temporal consciousness.

(Dalla Barba, 2002) and in other works from Dalla Barba's group, TC is meant to refer to individuals' phenomenological experience of remembering their past, of being present to their present world, and to predict episodes in their future. Craver et al. (2014, p. 192) say that "If TC is defined simply as the ability to remember past personal experiences and to episodically imagine future personal experiences, then KC—the well-know amnesic patient they describe in their work—lacks TC." Dalla Barba and co-worker's definition of TC refer exactly to this ability and not to the ability, which is preserved in amnesics, to access information concerning personal past, present and future. Craver et al. (2014) argue that episodic amnesia can spare many aspects of TC. KC had preserved semantic knowledge of time, he had little or no difficulties with physical, or chronological time and preserved order of succession judgement. In other words, KC had good knowledge of time:

> *"KC consciously understands the past, present and future, is aware of the fact that he has a past, present and future, and appreciates the implications of an event's being in the past, present or future (such as the temporal asymmetry of causation and the irrevocability of the past). If KC is trapped in the present, he is trapped there with an awareness of his past, present and future, that is, with temporal consciousness" (Craver et al., 2014, p. 193).*

Here and throughout their work the authors mistake KC (see above) for TC. An individual can be conscious *of* time, without having TC. KC allows individuals to know many things about personal time, to be aware that they have a past and a future, to arrange personal episodes along a timeline, to have attitudes about time, to make value judgements involving time, to know what regret is and to anticipate it. These operations are spared in KC, i.e., KC (and personal semantics, see above) is preserved. Yet none of these operations of KC grants the possibility of having the phenomenological experience of remembering their past, of being present to their present world, and of predicting episodes in their personal future, because these, according to the MCTT, are operations of TC, which is exactly what KC lacks. Knowledge of autobiographical facts, the ability to order autobiographical events on a timeline are preserved in most amnesics, but, as far as they lack phenomenological experience of remembering, they are not included in Dalla Barba's concept of TC. Autobiographical memories can be retrieved either in the mode of TC, i.e., with the phenomenological experience of remembering a specific personal past episode, or in the mode of KC, without the phenomenological experience of remembering a specific personal past episode. All KC's time-related spared abilities that Craver and colleagues attribute to aspects of TC are indeed aspects of KC (Dalla Barba, 2002). Patient RM, for example, was a young girl suffering from isolated retrograde amnesia, who had detailed knowledge of her autobiography, but who didn't have any phenomenological recollective experience of the episodes she could retrieve in the mode of KC (Dalla Barba et al., 1997c). This is an example of how autobiographical episodes can be retrieved in the mode of KC.

These apparent criticisms have forced us to recognize that our characterization of the phenomenon was imprecise and encompassed a wide range of temporal competencies that, in fact, are preserved in episodic amnesia.

Now, the next question is, to what extent the ideas described so far are compatible with existing theories on memory and confabulation?

A number of hypotheses have been proposed to account for confabulation.

The gap-filling account traditionally considers confabulation a more or less intentional desire to fill gaps in memory to avoid embarrassment (Bonhoeffer, 1904; Pick, 1905; Bleuler, 1949). This hypothesis has been disconfirmed by data showing that patients do not confabulate in any domain in which their memory is faulty or when they are asked to answer questions for which they have a mandatory gap in memory and for which both non-confabulating amnesics and normal subjects the "normal" response is "I don't Know" ("What did you do on March 13, 1985?", or "Who was the President of Mexico in 1975?" (Dalla Barba, 1993a; Dalla Barba et al., 1997b; Dalla Barba and Decaix, 2009; Schnider et al., 1996a). A related hypothesis is the one initially proposed by Conway and Tacchi (1996) and later developed by Fotopoulou et al. (2004, 2007), which states that confabulations are often motivated, guided by a wishful thinking, in order to embellish the patient's current situation. An argument in favor of this idea has been that confabulations often have a positive emotional content. Motivation and positive content of confabulation certainly occur in some cases and is not incompatible with the ideas we propose here. However, confabulations with negative, dark content have also been reported (Dalla Barba et al., 1998).

The executive dysfunction hypothesis has also been proposed to explain confabulation (Stuss et al., 1978; Kapur and Coughlan, 1980; Moscovitch and Melo, 1997). However, it has been shown that an executive/frontal dysfunction is neither necessary, nor sufficient for confabulation to occur (Dalla Barba et al., 1990, 1997a, 1999; Delbecq-Derouesné et al., 1990; Dalla Barba, 1993a).

Another group of theories proposes that confabulation is the result of a failure of monitoring processes. These theories hold that in confabulation processes involved in the evocation and verification of memories are impaired (Moscovitch, 1989, 1995; Johnson, 1991; Burgess and Shallice, 1996b; Moscovitch and Melo, 1997; Gilboa et al., 2006a; Schnider, 2008).

According to Johnson et al. (1997) confabulation reflects poor source monitoring, or reality monitoring, i.e., deciding whether a memory is a trace of something that actually happened to you, or is a memory of an imagined event. Impaired reality monitoring due to frontal damage would result in confabulation. However, it has been shown that reality monitoring was equally disrupted in a confabulatory patient and in non-confabulating patients with frontal lobe damage (Johnson et al., 1997). Accordingly, a reality monitoring deficit may occur with confabulation but is not the only factor involved in the genesis of confabulation (Johnson et al., 1997).

According to Moscovitch and colleagues (Moscovitch, 1989, 1995; Moscovitch and Melo, 1997; Gilboa et al., 2006a) confabulation results from the disruption of strategic retrieval, a monitoring, effortful, self-initiated cognitive process. If strategic retrieval is impaired due to orbitofrontal damage, memories are retrieved associatively, i.e., automatically, so that the first idea that comes to mind is accepted as a true memory, although it is actually a confabulation. A similar account of confabulation is proposed by other models (e.g., Burgess and Shallice, 1996a).

Within the group of monitoring theories of confabulation, Schnider and colleagues have proposed that confabulation is due to reality confusion resulting from a deficit of reality filtering following lesions to the posterior OFC (Brodman's area 13) or structures directly connected with it (Schnider and Ptak, 1999; Gilboa and Moscovitch, 2002). According to Schnider and colleagues, reality filtering describes a memory control process necessary to maintain thinking and behavior in phase with reality (Schnider, 2008). It depends on orbitofrontal area 13 and connected subcortical structures, is electrocortically expressed at 200–300 ms after evocation of a memory and is under dopaminergic modulation. They further argue that reality filtering can be traced back to extinction capacity, i.e., the ability to learn when previously valid anticipations no longer apply to current reality and behavior needs to be adapted (Nahum et al., 2010, 2011). A problem concerning this model, is the claim that filtering (monitoring) of evoked memories occurs at 200–300 ms. In our view it is quite difficult to understand how a memory, for example "Last night I had dinner at the restaurant", can be verified and subsequently accepted or rejected in such a short time. An additional problem is that Schnider's and colleagues experiments on confabulation are run in a time window of minutes (up to 30 min), whereas patients confabulate for episodes that occurred well beyond Schnider's and colleagues experimental time setting. Accordingly, it is questionable whether their experimental reduction can really be informative on the neurobiological and cognitive mechanisms underlying confabulation.

Taken together, theories that emphasize the disruption of monitoring/filtering processes in the origin of confabulation attribute to the frontal lobe, namely to the OFC, the role of searching and evaluating memories and information in the hippocampus and in the TPC. However, it is not specified on what theoretical basis the OFC would operate the search and evaluation of memory and information in the posterior part of the brain. In these theories the frontal cortex is assumed to have a subjective intentional life. Dalla Barba has indicated this as "the fallacy of the homunculus" (Dalla Barba, 2001, 2002), that is the idea that an unconscious subject, an *homunculus*, makes a selection between true and false memories and provide consciousness only with true memories. It is well known that patients with orbitofrontal lesions suffer from disinhibition, which involves not only memory, but the patient's entire behavior. Therefore it is reasonable to think that a disrupted OFC and related structures, provide the hippocampus, through the Papez circuit, with already distorted information that are temporalized as true memories and informations. This interpretation is more economical in that it avoids the involvement of strategic retrieval and monitoring processes,

which, at the state of the art, need to be more firmly theoretically grounded.

To summarize, the model described in this work is:

1. Compatible with current knowledge about functions and specialization of the human hippocampus. In particular, pattern separation and completion (e.g., Rolls, 2013; Deuker et al., 2014) and fine-grained local representations (e.g., Poppenk et al., 2013) may well be properties expressed in TC.
2. Internally coherent and theoretically grounded, without the need to postulate the existence of unconscious explanatory idols (Dalla Barba, 2009) like monitoring theories do.
3. Powerful in that it accounts in neurocognitive terms for amnesias and different forms of confabulation.

Unlike models which, being based on unconscious explanatory idols, are impermeable to scientific investigation, the account proposed here is scientifically falsifiable. Specifically, the present model will be disconfirmed if converging evidence will show that:

1. Patients with complete bilateral hippocampal damage are able to answer questions tapping TC. Questions like: "Do you remember what you had for dinner last night, the last time you went to the restaurant, the last time you went for a swim?", or "Can you predict when you will be going to the restaurant, for a swim next time?"
2. Patients with complete bilateral hippocampal destruction confabulate.
3. Patients who are amnesic for their personal past have phenomenological experience of their future.
4. Patients who confabulate in remembering their personal past do not confabulate when having phenomenological experience of their future.

Until converging counterevidence disconfirming the model will be provided, this, together with its central assumptions, should be considered a valuable account of existing knowledge and information concerning normal and pathological memory and its neurobiological bases.

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References

Addis, D. R., Cheng, T., Roberts, R. P., and Schacter, D. L. (2011). Hippocampal contribution to the episodic simulation of specific and future events. *Hippocampus* 21, 1045–1052. doi: 10.1002/hipo.20870

Alexander, M. P., and Freedman, M. (1984). Amnesia after anterior communicating artery aneurysm rupture. *Neurology* 34, 752–757. doi: 10.1212/wnl.34.6.752

Attali, E., De Anna, F., Dubois, B., and Dalla Barba, G. (2009). Confabulation in Alzheimer's disease: poor encoding and retrieval of over-mearned information. *Brain* 132, 204–212. doi: 10.1093/brain/awn241

Baddeley, A., and Wilson, B. (1986). "Amnesia, autobiographical memory and confabulation," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge, UK: Cambridge University Press), 225–252.

Benson, D. F., Djenderedjian, A., Miller, B. L., Pachana, N. A., Chang, L., Itty, L., et al. (1996). Neural basis of confabulation. *Neurology* 46, 1239–1243. doi: 10.1212/wnl.46.5.1239

Berlyne, N. (1972). Confabulation. *Br. J. Psychiatry* 120, 31–39. doi: 10.1192/bjp.120.554.31

Bleuler, E. (1949). *Lehrbuch der Psychiatrie.* Berlin: Springer Verlag.

Bonhoeffer, K. (1904). Der korsakowsche symptomenkoplex in seinen beziehungen zu den verschiedenen krankheitsformen. *All. Ztg. Psychiatrie* 61, 744–752.

Borsutzky, S., Fujiwara, E., Brand, M., and Markowitsch, H. J. (2008). Confabulations in alcoholic korsakoff patients. *Neuropsychologia* 46, 3133–3143. doi: 10.1016/j.neuropsychologia.2008.07.005

Botzung, A., Denkova, E., and Manning, L. (2008). Experiencing past and future personal events: functional neuroimaging evidence on the neural bases of mental time travel. *Brain Cogn.* 66, 202–212. doi: 10.1016/j.bandc.2007.07.011

Brentano, F. (1874). *Psychology from an Empirical Standpoint.* London: Routledge and Kegan Paul.

Burgess, P. W., and McNeil, J. E. (1999). Content-specific confabulation. *Cortex* 35, 163–182. doi: 10.1016/s0010-9452(08)70792-5

Burgess, P. W., and Shallice, T. (1996a). Bizarre response, rule detection and frontal lobe lesions. *Cortex* 32, 241–259. doi: 10.1016/s0010-9452(96)80049-9

Burgess, P. W., and Shallice, T. (1996b). Confabulation and the control of recollection. *Memory* 4, 359–411. doi: 10.1080/096582196388906

Cermak, L. S., Uhly, B., and Reale, L. (1980). Encoding specificity in the alcoholic korsakoff patient. *Brain Cogn.* 11, 119–127. doi: 10.1016/0093-934x(80)90115-7

Ciaramelli, E., and Ghetti, S. (2007). What are confabulators' memories made of? a study of subjective and objective measures of recollection in confabulation. *Neuropsychologia* 45, 1489–1500. doi: 10.1016/j.neuropsychologia.2006.11.007

Ciaramelli, E., Ghetti, S., Frattarelli, M., and Làdavas, E. (2006). When true memory availability promotes false memory: evidence from confabulating patients. *Neuropsychologia* 44, 1866–1877. doi: 10.1016/j.neuropsychologia.2006.02.008

Coltheart, M., Menzies, P., and Sutton, J. (2010). Abductive inference and delusional belief. *Cogn. Neuropsychiatry* 15, 261–287. doi: 10.1080/13546800903439120

Conway, M. A., and Tacchi, P. C. (1996). Motivated confabulation. *Neurocase* 2, 325–339. doi: 10.1080/13554799608402406

Craver, C. F., Kwan, D., Steindam, C., and Rosenbaum, R. S. (2014). Individuals with episodic amnesia are not stuck in time. *Neuropsychologia* 57, 191–195. doi: 10.1016/j.neuropsychologia.2014.03.004

Dalla Barba, G. (1993a). Confabulation: knowledge and recollective experience. *Cogn. Neuropsychol.* 10, 1–20. doi: 10.1080/02643299308253454

Dalla Barba, G. (1993b). Different patterns of confabulation. *Cortex* 29, 567–581. doi: 10.1016/s0010-9452(13)80281-x

Dalla Barba, G. (2001). Beyond the memory trace paradox and the fallacy of the homunculus: a hypothesis concerning the relation between memory, consciousness and temporality. *J. Conscious. Stud.* 8, 51–78.

Dalla Barba, G. (2002). *Memory, Consciousness and Temporality.* Boston: Kluver Academic Publishers.

Dalla Barba, G. (2009). "Temporal consciousnesss and confabulation: escape from unconscious explanatory idols," in *Confabulation–Views from Neuroscience, Psychiatry, Psychology and Philosophy*, ed. W. Hirstein (Oxford: Oxford University Press), 566–574.

Dalla Barba, G., and Boissé, M.-F. (2010). Temporal consciousness and confabulation: is the medial temporal lobe "temporal"? *Cogn. Neuropsychiatry* 15, 95–117. doi: 10.1080/13546800902758017

Dalla Barba, G., Boissé, M.-F., Bartolomeo, P., and Bachoud-Lévi, A.-C. (1997a). Confabulation following rupture of posterior communicating artery. *Cortex* 33, 563–570. doi: 10.1016/s0010-9452(08)70237-5

Dalla Barba, G., Cappelletti, Y. J., Signorini, M., and Denes, G. (1997b). Confabulation: remembering "another" past, planning "another" future. *Neurocase* 3, 425–436. doi: 10.1093/neucas/3.6.425-a

Dalla Barba, G., Mantovan, M. C., Ferruzza, E., and Denes, G. (1997c). Remembering and knowing the past: a case study of isolated retrograde amnesia. *Cortex* 33, 143–154. doi: 10.1016/s0010-9452(97)80010-x

Dalla Barba, G., Cipolotti, L., and Denes, G. (1990). Autobiographical memory loss and confabulation in korsakoff's syndrome: a case report. *Cortex* 26, 525–534. doi: 10.1016/s0010-9452(13)80302-4

Dalla Barba, G., and Decaix, C. (2009). "Do you remeber what you did on march 13 1985?" a case study of confabulatory hypermnesia. *Cortex* 45, 566–574. doi: 10.1016/j.cortex.2008.03.009

Dalla Barba, G., and La Corte, V. (2013). The hippocampus, a time machine that makes errors. *Trends Cogn. Sci.* 17, 102–104. doi: 10.1016/j.tics.2013.01.005

Dalla Barba, G., Mantovan, M. C., Cappelletti, Y. J., and Denes, G. (1998). Temporal gradient in confabulation. *Cortex* 34, 417–426. doi: 10.1016/s0010-9452(08)70764-0

Dalla Barba, G., Mantovan, M. C., Traykov, L., Rieu, D., Laurent, A., Ermani, M., et al. (2002). The functional locus of intrusions: encoding or retrieval? *J. Clin. Exp. Neuropsychol.* 24, 633–641. doi: 10.1076/jcen.24.5.633.1008

Dalla Barba, G., Nedjam, Z., and Dubois, B. (1999). Confabulation, executive functions and source memory in Alzheimer's disease. *Cogn. Neuropsychol.* 16, 385–398. doi: 10.1080/026432999380843

De Anna, F., Attali, E., Freynet, L., Foubert, L., Laurent, A., Dubois, B., et al. (2008). Intrusions in story recall: when over-learned information interferes with episodic memory recall. Evidence from Alzheimer's disease. *Cortex* 44, 305–311. doi: 10.1016/j.cortex.2006.08.001

Delbecq-Derouesné, J., Beauvois, M. F., and Shallice, T. (1990). Preserved recall versus impaired recognition. A case study. *Brain* 113, 1045–1174. doi: 10.1093/brain/113.4.1045

DeLuca, J., and Cicerone, K. D. (1991). Confabulation following aneurysm of the anterior communicating artery. *Cortex* 27, 417–423. doi: 10.1016/s0010-9452(13)80036-6

Deuker, L., Doeller, C. F., Fell, J., and Axmacher, N. (2014). Human neuroimaging studies on the hippocampal CA3 region–integrating evidence for pattern separation and completion. *Front. Cell. Neurosci.* 8:64. doi: 10.3389/fncel.2014.00064

Diamond, B. J., DeLuca, J., and Kelley, S. M. (1997). Memory and executive functions in amnesic and non-amnesic patients with aneurysms of the anterior communicating artery. *Brain* 120, 1015–1025. doi: 10.1093/brain/120.6.1015

Fotopoulou, A., Conway, M., and Solms, M. (2007). Confabulation: motivated reality monitoring. *Neuropsychologia* 45, 2180–2190. doi: 10.1016/j.neuropsychologia.2007.03.003

Fotopoulou, A., Solms, M., and Turbull, O. (2004). Wishful reality distortions in confabulation: a case report. *Neuropsychologia* 42, 727–744. doi: 10.1016/j.neuropsychologia.2003.11.008

Gabrieli, J., Cohen, N., and Corkin, S. (1988). The impairment of learning semantic knowledge following bilateral medial temporal lobe resection. *Brain Cogn.* 7, 157–177. doi: 10.1016/0278-2626(88)90027-9

Gascon, G. G., and Gilles, F. (1973). Limbic dementia. *J. Neurol. Neurosurg. Psychiatry* 36, 421–430. doi: 10.1136/jnnp.36.3.421

Gentilini, M., De Renzi, E., and Crisi, G. (1987). Bilateral paramedian thalamic artery infarcts: report of eight cases. *J. Neurol. Neurosurg. Psychiatry* 50, 900–909. doi: 10.1136/jnnp.50.7.900

Gilboa, A., Alain, C., Stuss, D. T., Melo, B., and Moscovitch, M. (2006a). Mechanism of spontaneous confabulations: a strategic retrieval account. *Brain* 129, 1399–1414. doi: 10.1093/brain/awl093

Gilboa, A., Winocur, G., Rosenbaum, R. S., Poreh, A., Gao, F., Black, S., et al. (2006b). Hippocampal contribution to recollection in retrograde and anterograde amnesia. *Hippocampus* 16, 966–980. doi: 10.1002/hipo.20226

Gilboa, A., and Moscovitch, M. (2002). "The cognitive neuroscience of confabulation: a review and a model," in *The Handbook of Memory Disorders*, eds A. Baddeley, M. Kopelman, and B. Wilson (Chichester: John Wiley and Sons Ltd), 315–342.

Hardt, O., Nader, K., and Nadel, L. (2013). Decay happens: the role of active forgetting in memory. *Trends Cogn. Sci.* 17, 111–120. doi: 10.1016/j.tics.2013.01.001

Hassabis, D., Kumaran, D., Vann, S., and Maguire, E. (2007). Patients with hippocampal amnesia cannot imagine new experiences. *Proc. Natl. Acad. Sci. U S A* 104, 1726–1731. doi: 10.1073/pnas.0610561104

Henke, K. (2010). A model of memory systems based on processing modes rather than consciuosness. *Nat. Rev. Neurosci.* 11, 523–532. doi: 10.1038/nrn2850

Hodges, J. R., and McCarthy, R. A. (1993). Autobiographical amnesia resulting from bilateral paramedian thalamic infarction. A case study in cognitive neurobiology. *Brain* 116(Pt. 4), 921–940. doi: 10.1093/brain/116.4.921

Husserl, E. (1893). *Zür Phänomenologie des Inneren Zietbewusstseins.* Milano: Franco Angeli.

Husserl, E. (1950). *Ideen zur Einen Reinen Phänomenologie.* Hen Haag: Martinus Nijhoff.

Ingvar, D. H. (1985). "Memory of the future": an essay on the temporal organization of conscious awareness. *Hum. Neurobiol.* 4, 127–136.

Irle, E., Wowra, B., Kunert, H. J., Hampl, J., and Kunze, S. (1992). Memory disturbances following anterior communicating artery rupture. *Ann. Neurol.* 31, 473–480. doi: 10.1002/ana.410310503

Johnson, M. K. (1991). "Reality monitoring: evidence from confabulation in organic brain disease patients," in *Awareness of Deficit After Brain Injury*, eds G. Prigatano and D. L. Schacter (New York-Oxford: Oxford University Press), 176–197.

Johnson, M. K., O'Connor, M., and Cantor, J. (1997). Confabulation, memory deficits and frontal dysfunction. *Brain Cogn.* 34, 189–206. doi: 10.1006/brcg.1997.0873

Kapur, N., and Coughlan, A. K. (1980). Confabulation after frontal lobe dysfunction. *J. Neurol. Neurosurg. Psychiatry* 43, 461–463. doi: 10.1136/jnnp.43.5.461

Kartsounis, L. D., and de Silva, R. (2011). Unusual amnesia in a patient with VGKC-Ab limbic encephalitis: a case study. *Cortex* 47, 451–459. doi: 10.1016/j.cortex.2010.01.009

Kern, R. S., Van Grop, W. G., Cummings, J. L., Brown, W. S., and Osato, S. S. (1992). Confabulation in Alzheimer's disease. *Brain Cogn.* 19, 172–182. doi: 10.1016/0278-2626(92)90043-L

Kikuchi, A., Chida, K., Misu, T., Okita, N., Takase, S., Nagata, T., et al. (1999). [A case of limbic encephalitis associated with breast cancer developed in an HTLV-1 carrier]. *Rinsho Shinkeigaku* 39, 555–559.

Klein, S. B., Loftus, J., and Kihlstrom, J. F. (2002). Memory and temporal experience. The effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. *Soc. Cogn.* 20, 353–379. doi: 10.1521/soco.20.5.353.21125

Knight, R. T., Grabowecky, M. F., and Scabini, D. (1995). Role of human prefrontal cortex in attention control. *Adv. Neurol.* 66, 21–34; discussion 34–36.

Kopelman, M. D. (1987). Two types of confabulation. *J. Neurol. Neurosurg. Psychiatry* 50, 1482–1487. doi: 10.1136/jnnp.50.11.1482

Kopelman, M. D., Guinan, E. M., and Lewis, P. D. R. (1995). Delusional memory, confabulation and frontal lobe dysfunction: a case study in De Clérambault's syndrome. *Neurocase* 1, 71–77. doi: 10.1093/neucas/1.1.71

Korsakoff, S. S. (1889). Etude médico-psychologique sur une forme des maladies de la mémoire. *Rev. Philos.* 28, 501–530.

Kremen, S. A., Solis, O. E., Shapira, J. S., Vinters, H. V., and Mendez, M. F. (2010). "Fantastic thinking" in pathologically proven pick disease. *Cogn. Behav. Neurol.* 23, 130–134. doi: 10.1097/WNN.0b013e3181df3007

Kwan, D., Carson, N., Addis, D. R., and Rosenbaum, R. S. (2010). Deficit in past remembering extend to future imagining in a case of developmental amnesia. *Neuropsychologia* 48, 3179–3186. doi: 10.1016/j.neuropsychologia.2010.06.011

La Corte, V., George, N., Pradat-Diehl, P., and Dalla Barba, G. (2011). Distorted temporal consciousness and preserved knowing consciousness in confabulation: a case study. *Behav. Neurol.* 24, 307–315. doi: 10.3233/BEN-2011-0341

La Corte, V., Serra, M., Boissé, M.-F., and Dalla Barba, G. (2010). Confabulation in Alzheimer's disease and amnesia: a qualitative account and a new taxonomy. *J. Int. Neuropsychol. Soc.* 16, 967–974. doi: 10.1017/S1355617710001001

Luria, A. R. (1976). *The Neuropsychology of Memory.* New York: John Wiley.

Markowitsch, H. J. (2008). Anterograde amnesia. *Handb. Clin. Neurol.* 88, 155–183. doi: 10.1016/S0072-9752(07)88007-9

Markowitsch, H. J., von Cramon, D. Y., and Schuri, U. (1993). Mnestic performance profile of a bilateral diencephalic infarct patient with preserved intelligence and severe amnesic disturbances. *J. Clin. Exp. Neuropsychol.* 15, 627–652. doi: 10.1080/01688639308402586

Martin, M. G. F. (2001). "Out of the past: episodic recall as retained acquaintance," in *Time and Memory*, eds C. Hoerl and T. McCormack (Oxford: Oxford University Press), 257–284.

Mercer, B., Wapner, W., Gardner, H., and Benson, F. (1977). A study of confabulation. *Arch. Neurol.* 34, 429–433. doi: 10.1001/archneur.1977.00500190063009

Merleau-Ponty, M. (1945). *Phénoménologie de la Perception.* Paris: Librairie Gallimard.

Moscovitch, M. (1989). "Confabulation and the frontal systems: strategic versus associative retrieval in neuropsychological theories of memory," in *Varieties of Memory and Consciousness: Essay in Honor of Endel Tulving*, eds H. L. Roediger and F. I. M. Craik (Hillsdale NJ: Lawrence Erlbaum), 133–160.

Moscovitch, M. (1995). "Confabulation," in *Memory Distortion*, eds D. L. Schacter, J. T. Coyle, G. D. Fischbach, M. M. Mesulam, and L. E. Sullivan (Cambridge: Harvard University Press), 226–251.

Moscovitch, M., and Melo, B. (1997). Strategic retrieval and the frontal lobes: evidence from confabulation and amnesia. *Neuropsychologia* 35, 1017–1034. doi: 10.1016/s0028-3932(97)00028-6

Mueller, S. G., Schuff, N., Yaffe, K., Madison, C., Miller, B., and Weiner, M. W. (2010). Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. *Hum. Brain Mapp.* 31, 1339–1347. doi: 10.1002/hbm.20934

Mueller, S. G., Stables, L., Du, A. T., Schuff, N., Truran, D., Cashdollar, N., et al. (2007). Measurement of hippocampal subfields and age-related changes with high resolution MRI at 4T. *Neurobiol. Aging* 28, 719–726. doi: 10.1016/j.neurobiolaging.2006.03.007

Nahum, L., Ptak, R., Leemann, B., Lalive, P., and Schnider, A. (2010). Behaviorally spontaneous confabulation in limbic encephalitis: the roles of reality filtering and strategic monitoring. *J. Int. Neuropsychol. Soc.* 16, 995–1005. doi: 10.1017/s1355617710000780

Nahum, L., Simon, S. R., Sander, D., Lazeyras, F., and Schnider, A. (2011). Neural response to the behaviorally relevant absence of anticipated outcomes and the presentation of potentially harmful stimuli: a human fMRI study. *Cortex* 47, 191–201. doi: 10.1016/j.cortex.2009.11.007

Nedjam, Z., Dalla Barba, G., and Pillon, B. (2000). Confabulation in a patient with frontotemporal dementia and in a patient with Alzheimer's disease. *Cortex* 36, 561–577. doi: 10.1016/s0010-9452(08)70538-0

Nedjam, Z., Devouche, E., and Dalla Barba, G. (2004). Confabulation, but not executive dysfunction discriminate AD from frontotemporal dementia. *Eur. J. Neurol.* 11, 728–733. doi: 10.1111/j.1468-1331.2004.00981.x

Papagno, C., and Muggia, S. (1996). Confabulation: dissociation between everyday life and neuropsychological performance. *Neurocase* 2, 111–118. doi: 10.1093/neucas/2.2.111

Pick, A. (1905). Zur psychologie der confabulation. *Neurologische Centralblatt* 24, 509–516.

Poppenk, J., Evensmoen, H. R., Moscovitch, M., and Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends Cogn. Sci.* 17, 230–240. doi: 10.1016/j.tics.2013.03.005

Rolls, E. T. (2013). The mechanisms for pattern completion and pattern separation in the hippocampus. *Front. Syst. Neurosci.* 7:74. doi: 10.3389/fnsys.2013.00074

Rosenbaum, R. S., Winocur, G., Grady, C., Ziegler, M., and Moscovitch, M. (2007). Memory for familiar environments learned in the remote past: fMRI studies of healthy people and amnesic person with extensive bilateral hippocampal lesions. *Hippocampus* 17, 1241–1251. doi: 10.1002/hipo.20354

Sandson, J., Albert, M. L., and Alexander, M. (1986). Confabulation in aphasia. *Cortex* 22, 621–626. doi: 10.1016/s0010-9452(86)80021-1

Sartre, J.-P. (1943). *L'être et le Néant.* Paris: Gallimard.

Schacter, D. L., and Addis, D. R. (2007). The cognitive neuroscience of constructive memory: remembering the past and imaging the future. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 362, 773–786. doi: 10.1098/rstb.2007.2087

Schacter, D. L., Addis, D. R., and Buckner, R. L. (2007). Remembering the past to imagine the future: the prospective brain. *Nat. Rev. Neurosci.* 8, 657–660. doi: 10.1038/nrn2213

Schnider, A. (2008). *The Confabulating Mind: How the Brain Creates Reality.* New York: Oxford University Press.

Schnider, A., Gutbrod, K., Hess, C. W., and Schroth, G. (1996a). Memory without context: amnesia with confabulations after infarction of the right capsular genu. *J. Neurol. Neurosurg. Psychiatry* 61, 186–193. doi: 10.1136/jnnp.61.2.186

Schnider, A., von Däniken, C., and Gutbrod, K. (1996b). The mechanisms of spontaneous and provoked confabulations. *Brain* 119, 1365–1375. doi: 10.1093/brain/119.4.1365

Schnider, A., and Ptak, R. (1999). Spontaneous confabulators fail to suppress currently irrelevant memory traces. *Nat. Neurosci.* 2, 677–681. doi: 10.1038/10236

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21 doi: 10.1136/jnnp.20.1.11

Serra, M., La Corte, V., Migliaccio, R., Brazzarola, M., Zannoni, I., Pradat-Diehl, P., et al. (2014). Confabulators mistake multiplicity for uniqueness. *Cortex* 58, 239–247. doi: 10.1016/j.cortex.2014.06.011

Stuss, D. T., Alexander, M. P., Lieberman, A., and Levine, H. (1978). An extraordinary form of confabulation. *Neurology* 28, 1166–1172. doi: 10.1212/wnl.28.11.1166

Suddendorf, T., and Corballis, M. C. (2007). The evolution of foresight: what is mental time travel and is it unique tu humans? *Behav. Brain Sci.* 30, 299–351. doi: 10.1017/s0140525x07001975

Talland, G. A. (1961). Confabulation in the wernicke-korsakoff sindrome. *J. Ner. Ment. Dis.* 132, 361–381. doi: 10.1097/00005053-196105000-00001

Trepel, C., and Racine, R. J. (1998). Long-term potentiation in the neocortex of the adult, freely moving rat. *Cereb. Cortex* 8, 719–729. doi: 10.1093/cercor/8.8.719

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi: 10.1037/h0080017

Tulving, E. (2002). "Chronestesia: awareness of subjective time," in *Principles of Frontal Lobe Functions*, eds D. T. Stuss and R. C. Knight (New York: Oxford University Press), 311–325.

Victor, M., Adams, R. D., and Collins, G. H. (1971). *The Wernicke-Korsakoff Syndrome.* Phildelphia: Davis.

Weinstein, E. A., and Lyerly, O. G. (1968). Confabulation following brain injury. *Arch. Gen. Psychiatry* 18, 348–354. doi: 10.1001/archpsyc.1968.01740030092009

Wyke, M., and Warrington, E. (1960). An experimental analysis of confabulation in a case of korsakoff's syndrome using a tachistoscopic method. *J. Neurol. Neurosurg. Psychiatry* 23, 327–333. doi: 10.1136/jnnp.23.4.327

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Integrating events across levels of consciousness

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Our knowledge grows as we integrate events experienced at different points in time. We may or may not become aware of events, their integration, and their impact on our knowledge and decisions. But can we mentally integrate two events, if they are experienced at different time points and at different levels of consciousness? In this study, an event consisted of the presentation of two unrelated words. In the stream of events, half of events shared one component ("tree desk" ... "desk fish") to facilitate event integration. We manipulated the amount of time and trials that separated two corresponding events. The contents of one event were presented subliminally (invisible) and the contents of the corresponding overlapping event supraliminally (visible). Hence, event integration required the binding of contents between consciousness levels and between time points. At the final test of integration, participants judged whether two supraliminal test words ("tree fish") fit together semantically or not. Unbeknown to participants, half of test words were episodically related through an overlap ("desk"; experimental condition) and half were not (control condition). Participants judged episodically related test words to be closer semantically than unrelated test words. This subjective decrease in the semantic distance between test words was both independent of whether the invisible event was encoded first or second in order and independent of the number of trials and the time that separated two corresponding events. Hence, conscious and unconscious memories were mentally integrated into a linked mnemonic representation.

Keywords: episodic memory, unconscious, masking, subliminal, associations, flexibility, compositionality, memory systems

INTRODUCTION

No event equals another event. But events may share aspects such as a person or an item in the scene. Such commonalities between events help us to bridge events, to integrate information from events, and to make inferences that guide our choices in new situations. We are usually aware of the events that we experience. But the act of our mental integration of memories of several events and its impact on our choices and behaviors may escape our awareness. While most past experiments aimed at investigating memory for single, discrete events, there is mounting evidence that (conscious) memories of multiple events are integrated into networks, which form the basis of inference (Heckers et al., 2004; Preston et al., 2004; Smith and Squire, 2005; Shohamy and Wagner, 2008; Zeithamova and Preston, 2010; Zeithamova et al., 2012). In some experiments, integration and inference were unconscious but the encoding of events was conscious (Greene et al., 2001, 2006; Leo and Greene, 2008). In other experiments, all mental processes were unconscious, namely the processing of subliminal (invisible) events, their mental integration, and resulting inference as measured behaviorally in a test situation (Reber and Henke, 2012; Reber et al., 2012).

Neuroimaging studies in volunteers showed that the hippocampus, a brain structure that is crucial for episodic memory (Tulving, 2002; Squire, 2004), was activated when overlapping events (i.e., events with common components) were experienced and/or when inferences were made in the test situation (Heckers et al., 2004; Preston et al., 2004; Greene et al., 2006; Shohamy and Wagner, 2008; Zeithamova and Preston, 2010; Reber et al., 2012; Zeithamova et al., 2012). Importantly, the hippocampus assisted these mental operations even when they occurred outside conscious awareness (Reber et al., 2012).

A fundamental question concerns whether and how conscious and unconscious memories interact. We ask whether the mental integration of discrete events is possible if consciousness divides between events. This may happen if a first event is experienced consciously, while a second event is experienced unconsciously; or vice versa. We hypothesized that two discrete, overlapping events can be bridged through integration of memory traces across consciousness levels because evidence indicates that memories of unconsciously and consciously experienced events are laid down in the same memory system, namely the hippocampus and related cortices (Henke et al., 2003; Degonda et al., 2005; Reber et al., 2012). Hence interactions between conscious and unconscious memory traces in this study are thought to occur within the same memory system and not between different memory systems. Earlier reports of implicit-explicit interactions concerned psychologically and neuroanatomically separate memory systems that either cooperated or competed in the process of learning a material or a certain procedure (Wagner et al., 2000; Poldrack et al., 2001; Voermans et al., 2004; Moses et al., 2010). Here,

we study implicit-explicit interactions within a single memory system, namely episodic memory or the medial temporal lobe memory system, whose output is either accessible or inaccessible to conscious awareness depending on the input – subliminal versus supraliminal. We expect conscious and unconscious memory representations to be integrated into a cohesive memory space that guides choices in a test situation.

An event was operationalized as the visual presentation of two unrelated words, such as "tree desk." In the case of "unconscious events," word pairs were presented subliminal, i.e., for 17 ms and flanked by pattern masks. In the case of "conscious events," word pairs were presented supraliminal (visible). Half of word pairs shared one word, e.g., "tree desk" and "desk fish," and were therefore overlapping (experimental condition). The other half of word pairs was non-overlapping because they shared no words (control condition) (**Figure 1**). To examine whether integration success is modulated by intervening time and trials, we varied the number of word pairs that intervened two overlapping word pairs by presenting 1, 5, 9, or 13 word pairs in-between. Of the two corresponding word pairs, the first was presented subliminal and the second supraliminal to half of participants, reversed for the other half of participants. We hypothesized that overlapping events would be integrated across consciousness levels irrespective of whether the first or the second event was processed consciously. Either way, a successful integration of word pairs across events and across consciousness levels presupposes that within-event associations be established. The test of integration was given 1 min following encoding. This test required participants to judge whether two supraliminal words fit together semantically or not. The two test words were either unrelated (control condition) or episodically related (e.g., "tree fish") through two distinct events ("tree desk"... "desk fish") that shared one word (experimental condition) (**Figure 1**). Words in test pairs of both conditions had been seen during encoding; one word with and the other word without consciousness. The only difference between conditions was the unconscious episodic link between test words. The mental integration of overlapping events was expected to change the speed of participants' decisions and/or the outcome

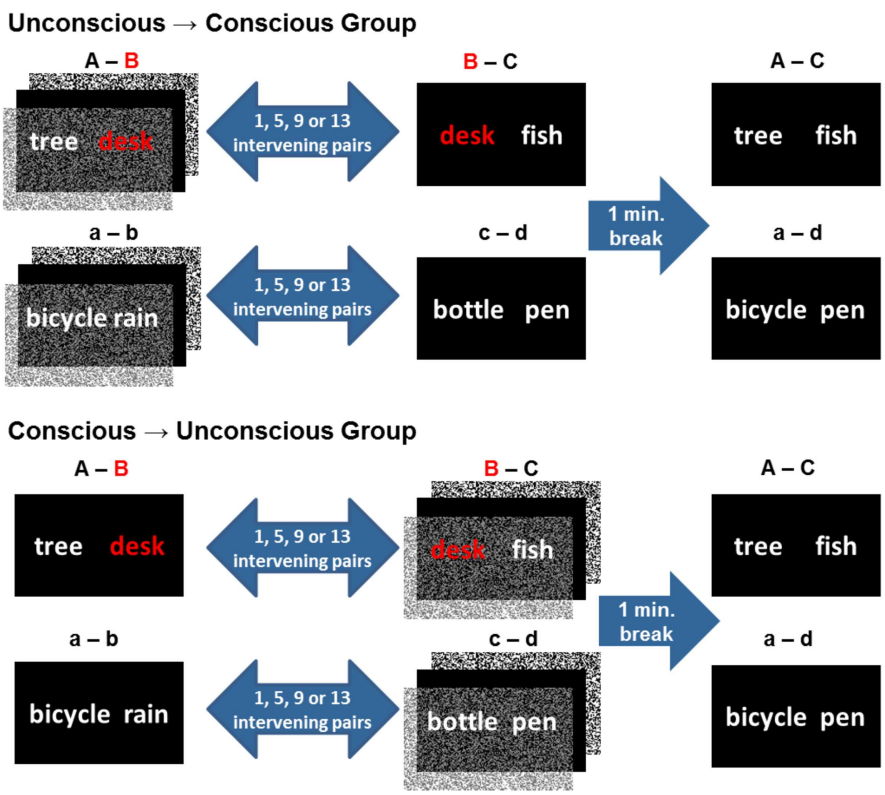


FIGURE 1 | Design. An event consisted of the presentation of two unrelated words. Participants experienced two overlapping (experimental condition; overlap indicated in red) or non-overlapping (control condition) encoding events. The temporal distance and amount of distraction given between two corresponding overlapping and non-overlapping events was varied in four levels with 1, 5, 9, or 13 word pairs presented in-between. Depending on the group assignment, either the first or the second encoding event was presented subliminal for unconscious encoding. The subliminal presentation mode is graphically illustrated by forward and backward pattern masks. We refer to overlapping word pairs presented in the experimental condition as A–B and B–C and to non-overlapping word pairs presented in the control condition as a–b, c–d. Words in test events were presented supraliminal. A and C words from the two encoding events were re-presented at test to induce the retrieval of the common counterpart (B) in the experimental condition. In the control condition, a and d words were re-presented at test, each of which could activate its respective counterpart (b or c), but no common counterpart. Hence retrieval words given in the control condition were not episodically related by a word that was part of both encoding events.

of their decisions at test (Reber and Henke, 2012; Reber et al., 2012).

MATERIALS AND METHODS

PARTICIPANTS

Sixty students participated in the study (age: 19–35 years, $M = 22.95$, SD = 3.10; 40 women; six left-handers). At the point of testing, all participants had already 12 years of education. Exclusion criteria were a native language other than German, suboptimal visual acuity, a history of neurological or psychiatric disorders, and the consumption of legal or illegal drugs. Participants were kept naïve regarding the study purpose and the presentation of subliminal stimuli. We misinformed participants initially that we investigated attention and word processing alone, but participants were fully debriefed following the main experiment. The study was approved by the local ethics committee.

MATERIALS AND DESIGN

The 384 German nouns of the main experiment were arranged to 192 semantically unrelated pairs that we presented to participants for conscious and unconscious encoding. These 192 word pairs were divided into two stimulus lists: one list was used for the experimental and the other for the control condition (96 word pairs per list/condition). Word overlaps were introduced in 48 couples of pairs (short hand: A–B, B–C; **Figure 1**) in list 1, which half of participants received for integrative encoding in their experimental condition. This half of participants received the 96 non-overlapping word pairs (short hand: a–b, c–d; **Figure 1**) of list 2 for non-integrative encoding in their control condition. The other half of participants received list 1 in the control condition and list 2 in the experimental condition. Accordingly, word overlaps were introduced in the 48 couples of pairs in list 2 for integrative encoding, while word pairs in list 1 were left non-overlapping. Importantly, all participants received the same word pairs for retrieval, counterbalanced between conditions. Hence, words in a given retrieval word pair were episodically related for half of participants (experimental condition) but unrelated for the other half of participants (control condition). Retrieval word pairs in both conditions consisted of the left-hand word of the first encoding word pair followed by the right-hand word of the corresponding second encoding word pair.

Stimuli of the experimental and the control condition were assigned to 12 sets that were used in 12 encoding-retrieval runs (**Figure 2**). Each run contained eight overlapping encoding word pairs in the experimental condition (A–B, B–C), eight non-overlapping encoding word pairs in the control condition (a–b, c–d), and four retrieval word pairs both in the experimental condition (A–C) and the control condition (a–d). The assignment of the 12 stimulus sets to runs was random. The practice run given before the main experiment was designed identical to the 12 experimental runs.

APPARATUS

The experiment took place in a dark room. A digital light processing (DLPTM) video beamer with a refresh rate of 60 Hertz projected the stimuli on a white screen positioned 2 m in front of the participant. The participant sat in a chair with his/her head fixated on a chin rest. The stimulated visual field spanned 10 (height) × 13 (width) degrees. For stimulus presentation we used the software Presentation ®(http://www.neurobs.com/). All responses were recorded with a standard computer mouse.

PROCEDURE

Encoding

The first encoding word pair was presented subliminal and the corresponding second word pair supraliminal for half of participants ("unconscious → conscious group") and vice versa for the other half of participants ("conscious → unconscious group") (see **Figure 2**). If word pairs appeared supraliminal (presentation duration: 3.5 s; inter-stimulus interval: 1 s), participants decided for each pair whether the two words fit together semantically or not (fit/don't fit task). This task invokes mental comparison processes that provide for incidental paired-associative semantic encoding of words. Because words in pairs were not closely associated semantically, participants were encouraged to relax their response criterion to arrive at about 50% fit responses. Participants were informed that closely related words such as "needle – yarn" would not be presented. Instead, word pairs such as "cow – grill" would be presented. Although such words are rather remote semantically, they may still elicit a "fit" answer because beef for example is a popular sort of meat for barbecues.

When word pairs were subliminal, participants perceived a flickering stream of pattern masks and simultaneously performed an attention task on images that were embedded in the sequence of subliminal words and pattern masks. We used the masking paradigm of our previous studies on subliminal encoding (Degonda et al., 2005; Duss et al., 2011; Reber and Henke, 2011, 2012; Reber et al., 2012; see "Subliminal Stimulus Presentation and Attention Task"). An instruction slide presented before the block of eight subliminal encoding pairs and the block of eight supraliminal encoding pairs prepared participants for their up-coming task (**Figure 2**). Time and trials between two corresponding word pairs were manipulated; we presented 1, 5, 9, or 13 word pairs in-between two corresponding encoding word pairs (**Figure 2**). Word pairs were randomly assigned to interval levels. Following encoding, participants took a 1-min break that served as a mini consolidation phase.

Retrieval

To test for relational integration, we presented four retrieval pairs in each condition. The order of these eight pairs was randomly generated for each participant and each run. Retrieval word pairs were presented in the same fashion (presentation duration: 3.5 s; inter-stimulus interval: 1 s) and with the same task (fit/don't fit task) as supraliminal encoding word pairs.

Subliminal stimulus presentation and attention task

We used the masking paradigm of our previous studies on subliminal encoding (Degonda et al., 2005; Duss et al., 2011; Reber and Henke, 2011, 2012; Reber et al., 2012). Each encoding word pair was flashed 12 times for 17 ms within a time window of 6 s that constituted one encoding trial. Word pairs were flanked by black and white dot pattern masks that were presented for 183 ms. In this

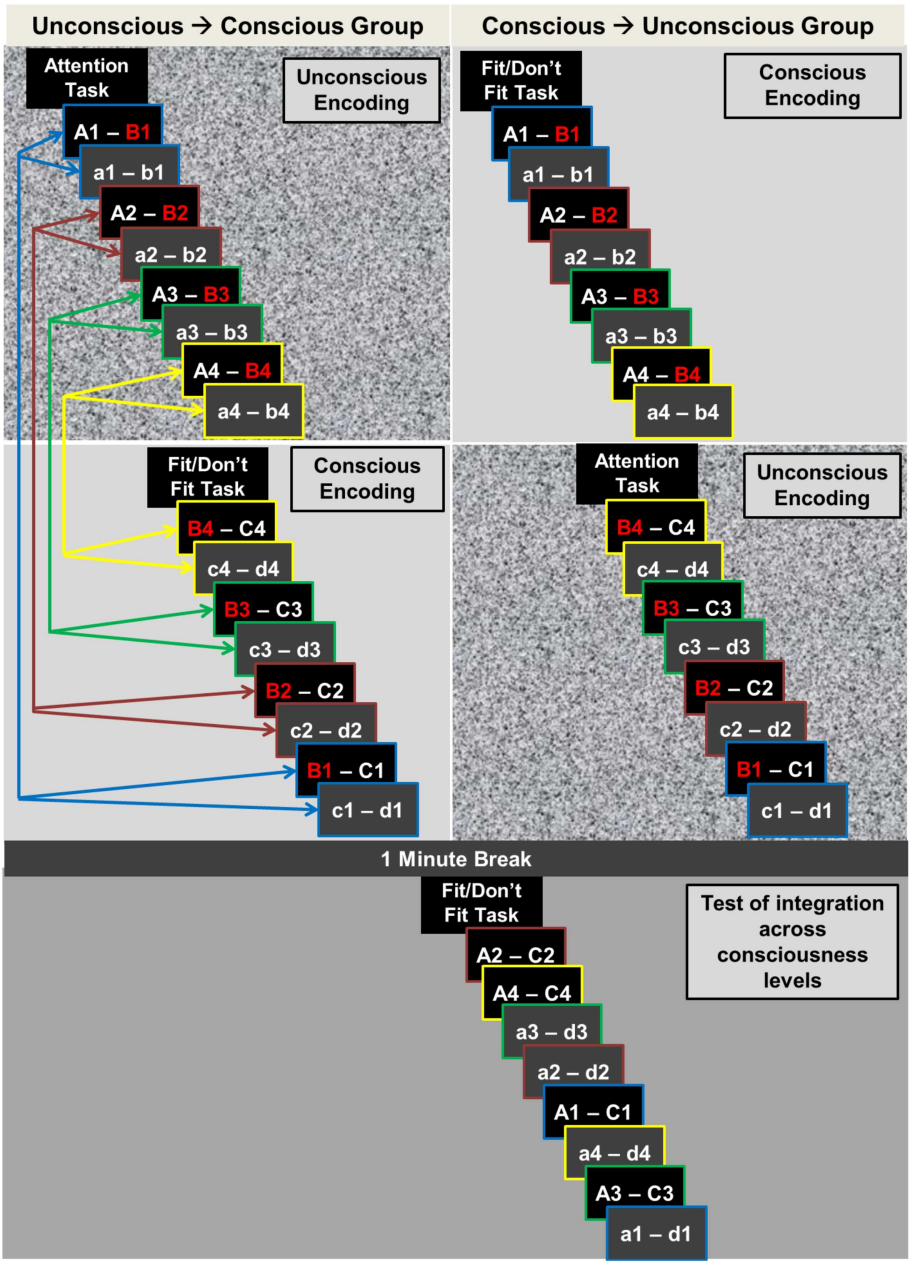


FIGURE 2 | Experimental procedure. The experiment consisted of 12 encoding-test runs. Here, we illustrate the procedure of one run. For the unconscious → conscious group (left-hand upper panel), the first encoding word pair (A–B and a–b) was presented subliminally (illustrated by the visual noise background) and the second, corresponding encoding word pair supraliminally (B–C and c–d). This order was reversed for the conscious → unconscious group of participants (right-hand upper panel). Corresponding encoding word pairs were overlapping in the experimental condition (A–**B**, **B**–C; overlaps depicted in red) and non-overlapping in the control condition (a–b, c–d). The distance between two corresponding encoding word pairs was varied fourfold with 1, 5, 9, or 13 intervening word pairs. The four distance levels are highlighted with color-coded arrows and color-coded image-frames. The same distances applied to the procedure in the conscious → unconscious group (arrows are omitted in right-hand panel). A break of 1 min separated encoding and test. Test trials of the experimental and the control condition were presented in random order and with supraliminal duration for participants in both groups. Both in supraliminal encoding and supraliminal test trials, participants decided whether the two words of a pair fit together semantically or not. During subliminal trials, participants performed an attention task.

stream of subliminal word pairs and pattern masks, we embedded an attention task for participants to stay focused and direct gaze at the screen center. The attention task required participants to fixate a repeatedly flashed central fixation cross and to indicate when the fixation cross was replaced by a horizontal or vertical line segment (push left or right key, respectively). The fixation cross was

presented for 233 ms at a rate of one Hertz. The fixation cross was replaced only once by a line segment at a random time point within the 6-s time window that constituted a trial.

TEST OF AWARENESS

Following the main experiment, participants underwent a structured interview to find out whether they had noticed or suspected the presence of subliminal stimuli in the experiment. Next, participants were informed of subliminal word pairs in the experiment. Finally, they took an objective awareness test to assess their ability to consciously discern subliminal word pairs or fragments thereof. Participants were instructed to try to discern a subliminal word pair and to match it to a subsequently presented identical or different word pair on a trial-by-trial basis. While instructions in the main experiment were indirect not alluding to subliminal word pairs, instructions in the test of awareness were direct. Direct tests are predominantly sensitive to conscious rather than unconscious processes (Reingold and Merikle, 1988; Snodgrass and Shevrin, 2006) and therefore yield a measure of conscious access to subliminal stimuli. Indirect tests are predominantly sensitive to unconscious rather than conscious processes. We aimed at indirectly measured effects of unconscious processing with no directly measured effects of conscious word detection (Reingold and Merikle, 1988; Greenwald et al., 1995). The test of awareness was different for the two experimental groups because subliminal words (B words in B–C pairs) were primed by previously perceived supraliminal words (A–B pairs) in the conscious → unconscious group but not the unconscious → conscious group.

Test of awareness for the unconscious → conscious group

The test of awareness included 96 trials. Each trial consisted of the subliminal presentation of one word pair followed by the supraliminal presentation of either the same or a different word pair (**Figure 3**). The masking paradigm and psychophysical conditions applied in the main experiment were again applied in the test of awareness. Participants were instructed to attend to the subliminal presentation of a word pair, while doing the attention task, and then to indicate by button press whether the subsequently presented visible word pair corresponded to the subliminal word pair (target) or not (distractor). Supraliminal targets and distractors stayed on the screen till participants responded. The probability of targets was 50%.

Test of awareness for the conscious → unconscious group

This awareness test included 96 trials as well, but these trials were divided into six runs that each contained 16 subliminal-supraliminal test trials. As in this group's main experiment, each run started off with the supraliminal presentation of eight A–B word pairs for participants to decide whether words in a pair fit together or not (fit/don't fit task). This preactivation was followed by the 16 subliminal-supraliminal test trials. The presentation order of the 16 trials was randomized. Eight of the 16 trials contained subliminal pairs with a primed B word (B–C trials)

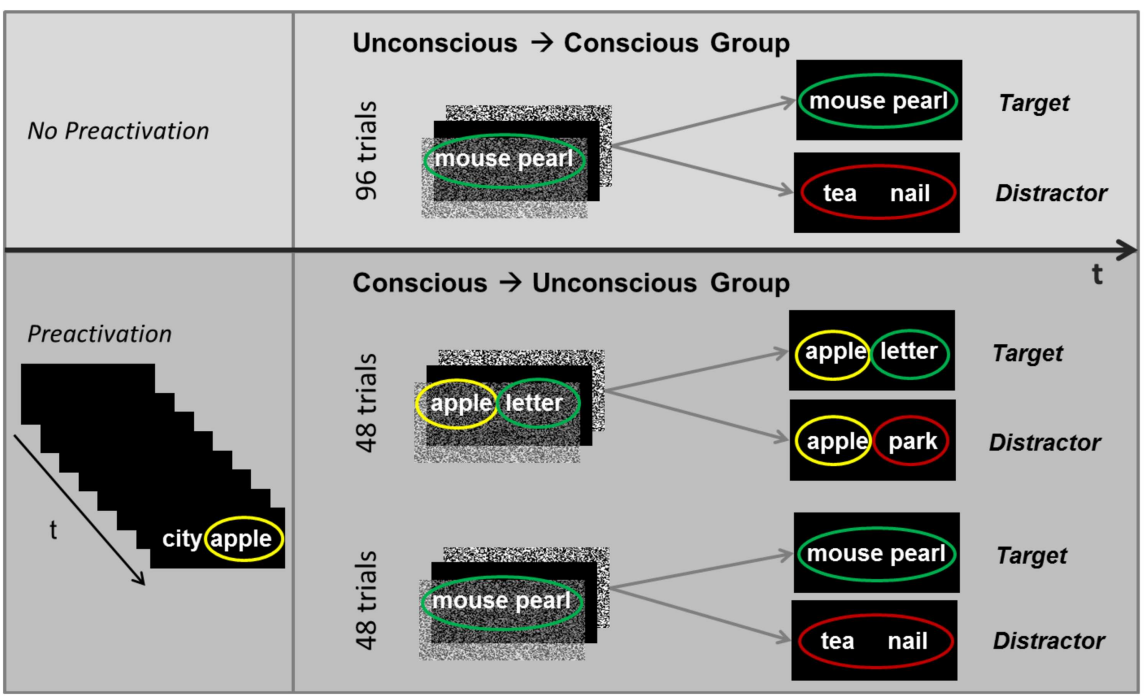


FIGURE 3 | Design of the test of awareness. Following the main experiment, participants took an objective awareness test to assess their ability to consciously discern subliminal word pairs or fragments thereof. Participants were instructed to try to discern a subliminal word pair and to match it to a subsequently presented identical (target) or different (distractor) word pair on a trial-by-trial basis. The test of awareness was different for the two experimental groups because subliminal words (B words in B–C pairs) were primed by previously perceived supraliminal words (A–B pairs) in the conscious → unconscious group (bottom panel) but not the unconscious → conscious group (top panel). *t*, time.

and eight trials contained subliminal pairs with unprimed words (**Figure 3**). Each of the subliminally presented word pairs was immediately followed by a supraliminal word pair (target or distractor) for participants to indicate by button press whether the visible word pair was identical to the subliminal word pair or not. In trials where subliminal word pairs were unprimed, targets were equal to subliminal words and distracters differed (as for the unconscious → conscious group). However, in trials where the first word in a subliminal pair was primed (e.g., apple), targets were equal to subliminal words, while distractors were composed of the same first word (e.g., apple) plus a second new word (e.g., park) (**Figure 3**). Hence, both targets and distractors contained the primed word (e.g., apple). This circumstance allowed us to test only for the perceptual processing of subliminal new words that were presented besides the primed words in pairs. Hence, with this procedure we could not test for a perceptual advantage of the primed words contained in subliminal pairs. Even if only the targets, but not the distractors, would contain a primed word (e.g., apple), participants' selections would still fail to indicate whether the subliminal processing of primed words is facilitated because the absence versus presence of a previously seen (during preactivation) and probably remembered word would skew selections in favor of targets.

STATISTICAL ANALYSES

For the analysis of performance accuracy at test, we computed the rate of each participant's fit responses to A–C pairs (experimental condition) and to a–d pairs (control condition) by dividing the total of fit responses by the respective total of given responses. The rate of fit responses was also computed for each encoding interval (1, 5, 9, or 13 word pairs between two corresponding encoding word pairs; see **Figure 2**). Trials with RTs below 500 ms were excluded. Rates of fit responses were analyzed in an ANOVA with the two within-subjects factors Condition (experimental versus control condition) and Encoding Interval (1, 5, 9, or 13 intervening word pairs) and the between-subjects factor Encoding Order (unconscious → conscious versus conscious → unconscious). For the analysis of reaction latency, RTs of fit and don't fit responses were z-transformed with respect to the RT distribution of each participant. RTs with z-values deviating more than 2 SDs from a participant's mean were excluded. We computed each participant's mean RT for A–C pairs (experimental condition) and a–d pairs (control condition) and per encoding interval. Mean RTs were analyzed in an ANOVA that included the same factors as the ANOVA used for the accuracy data (rate of fit responses).

We also computed mean RTs of fit and don't fit responses to supraliminal encoding word pairs. For participants of the conscious → unconscious group, supraliminal encoding word pairs were A–B and a–b word pairs. For participants of the unconscious → conscious group, supraliminal encoding word pairs were B–C and c–d word pairs. Differences in mean RT between conditions were tested for significance with a paired-samples t-test.

RESULTS

TEST OF AWARENESS: PERFORMANCE AT CHANCE LEVEL

As in the main experiment, trials with RTs below 500 ms were excluded from the analysis. Rates of correct answers (hits plus correct rejections) in the test of awareness deviated from chance performance (0.50) neither in the unconscious → conscious group [$M \pm \mathrm{SE} = 0.51 \pm 0.01$; $t(29) = 0.969$, $p = 0.341$; 96 trials] nor the conscious → unconscious group [$M \pm \mathrm{SE} = 0.50 \pm 0.01$; $t(29) = -0.407$, $p = 0.687$; 96 trials]. Discrimination performance in the latter group remained at chance level, when preactivation trials [$M \pm \mathrm{SE} = 0.49 \pm 0.01$; $t(29) = -0.601$, $p = 0.553$] and trials without preactivation [$M \pm \mathrm{SE} = 0.50 \pm 0.01$; $t(29) = 0.158$, $p = 0.876$] were analyzed separately.

Binomial tests computed for every participant revealed that two of the 60 participants yielded a relatively good discrimination performance that reached a probability of 10% or lower (one-tailed) to be obtained by chance alone. Furthermore, one participant reported to have consciously perceived subliminal letters during the main experiment. However, this person's performance in the test of awareness was at chance level. We decided to exclude these three participants from the analysis of the data from the main experiment. Accordingly, 28 participants remained in the unconscious → conscious group and 29 in the conscious → unconscious group.

CONSCIOUS AND UNCONSCIOUS ENCODING OF EVENTS

Good accuracy on the attention task

Performance accuracy on the attention task given during subliminal trials was good and did not differ between the two experimental groups [$t(37.956) = -0.982$, $p = 0.332$, adjusted degrees of freedom because equality of variances was not assumed]. The unconscious → conscious group yielded a hit rate of 0.88 ± 0.02 ($M \pm \mathrm{SE}$) and the conscious → unconscious group of 0.90 ± 0.01 ($M \pm \mathrm{SE}$).

Subliminal B words in A–B pairs primed supraliminal B words in B–C pairs

As a consequence of the encoding of subliminal A–B pairs in the unconscious → conscious group, we expected a facilitated processing (priming) in the experimental condition, where B words were repeated in supraliminal B–C pairs. A premise of B word priming is a compositional rather than unitized representation of B words in A–B and B–C pairs. A compositional mental representation allows both for the reactivation of each individual part in a representation (A; B) and the reactivation of the complete representation (A–B). A unitized mental representation, however, would require the repeated visual presentation of the complete initial word pair (A–B), not just the B word, to trigger a reactivation of the previously formed A–B representation. Our data spoke for a compositional representation of subliminal A–B pairs. Responses to supraliminal B–C pairs were faster ($M \pm \mathrm{SE} = 2106 \pm 71$ ms) than responses to supraliminal c–d pairs ($M \pm \mathrm{SE} = 2163 \pm 78$ ms) [$t(27) = 3.502$, $p = 0.002$, $r^2 = 0.312$]. The absence of a corresponding difference in the processing speed of supraliminal A–B ($M \pm \mathrm{SE} = 2138 \pm 68$ ms) versus supraliminal a–b pairs ($M \pm \mathrm{SE} = 2147 \pm 65$ ms) [$t(28) = 0.440$, $p = 0.663$] in the conscious → unconscious group substantiates the interpretation in terms of priming.

TEST PERFORMANCE: SUCCESSFUL INTEGRATION OF EVENTS

We computed an ANOVA with the two within-subjects factors Condition and Encoding Interval as well as the between-subjects

factor Encoding Order. The dependent variable was the rate of fit responses given at test. This ANOVA yielded a significant main effect of Condition (**Figure 4**). Participants gave more fit responses to episodically related A–C pairs ($M \pm SE = 0.38 \pm 0.02$) versus unrelated a–d pairs ($M \pm SE = 0.36 \pm 0.02$), $F(1,55) = 5.310$, $p = 0.025$, $\eta^2_{partial} = 0.088$. This effect of Condition interacted neither with Encoding Interval [$F(3,165) = 0.011$, $p = 0.999$] nor with Encoding Order [$F(1,55) = 0.263$, $p = 0.610$]. There was no main effect of Encoding Interval [$F(3,165) = 0.234$, $p = 0.872$], no significant interaction of Encoding Interval with Encoding Order [$F(3,165) = 1.156$, $p = 0.328$], and no three-way interaction of Condition with Encoding Interval and Encoding Order [$F(3,165) = 0.379$, $p = 0.768$]. The means (±SE) of the rate of fit responses were almost identical between encoding intervals (1 pair, 5 pairs, 9 pairs, 13 pairs) both for the experimental condition ($M_{1pair} = 0.38 \pm 0.03$; $M_{5pairs} = 0.38 \pm 0.02$; $M_{9pairs} = 0.38 \pm 0.02$; $M_{13pairs} = 0.40 \pm 0.02$) and the control condition ($M_{1pair} = 0.36 \pm 0.02$; $M_{5pairs} = 0.36 \pm 0.02$; $M_{9pairs} = 0.36 \pm 0.02$; $M_{13pairs} = 0.37 \pm 0.03$). However, the between-subjects factor Encoding Order reached significance [$F(1,55) = 5.294$, $p = 0.025$, $\eta^2_{partial} = 0.088$]. A potential reason for this main effect might be the unconscious → conscious group's criterion for generating fit responses, which might be looser yielding more fit responses ($M \pm SE = 0.41 \pm 0.02$) than the conscious → unconscious group ($M \pm SE = 0.34 \pm 0.02$). In support of this interpretation, the unconscious → conscious group also generated more fit responses during supraliminal encoding (B–C and c–d pairs; $M \pm SE = 0.45 \pm 0.02$) than the conscious → unconscious group (A–B and a–b pairs; $M \pm SE = 0.36 \pm 0.02$) [$t(52.605) = 3.256$, $p = 0.002$, $r^2 = 0.167$, adjusted degrees of freedom because equality of variances was not assumed].

Reaction latencies at test were comparable between the experimental (A–C; $M \pm SE = 1942 \pm 46$ ms) and the control condition [a–d; $M \pm SE = 1952 \pm 45$ ms; $t(56) = 0.854$, $p = 0.397$]. This absence of an integration effect on reaction speed was also reflected in the non-significance of all results of an ANOVA that included the same factors as the ANOVA on the rates of fit responses (all Fs < 2.469, all ps > 0.122). Hence, the mental integration of events across levels of consciousness influenced the type but not the speed of responses given at test.

CONSCIOUS WORD DISCRIMINATION DID NOT ASSIST THE UNCONSCIOUS INTEGRATION OF EVENTS

Using the regression method described by Greenwald et al. (1995), we found that discrimination performance in the test of awareness [(hits + correct rejections) − (false alarms + misses)] was not significantly associated with the increase in the rate of fit responses given to episodically related versus unrelated test words [$B = -0.314 \pm 0.184$, $\beta = -0.224$, $t(55) = -1.705$, $p = 0.094$; $N = 57$]. However, the y-axis intercept in this regression was significantly larger than zero [intercept $= 0.023 \pm 0.010$; $t(55) = 2.309$, $p = 0.025$, $r^2 = 0.088$]. This indicates that the unconscious integration of events was significant, when discrimination performance in the test of awareness was zero (**Figure 4**).

DISCUSSION

We asked whether the mental integration of discontiguous events is possible if consciousness divides between events because one event is experienced consciously and the other unconsciously. An event was operationalized as the visual presentation of two unrelated words that were either presented supraliminal for conscious inspection or subliminal for unconscious processing. At the test

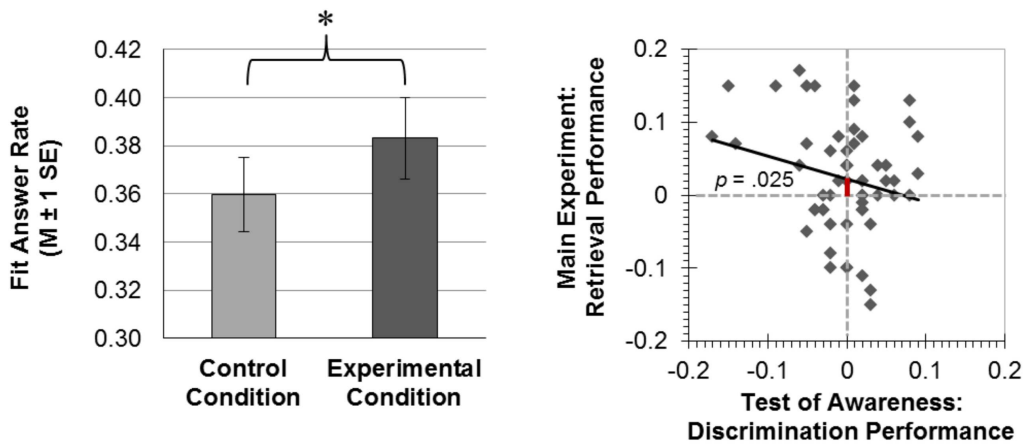


FIGURE 4 | Results. Left-hand panel: at the test of integration across consciousness levels, participants gave more fit answers in the experimental than the control condition (*$p < 0.05$; M, mean; SE, standard error of the mean). Subliminal and supraliminal encoding word pairs had shared a word in the experimental condition, which lent these word pairs to integration that manifested in biased semantic decisions at test (more fit responses). Right-hand panel: using the regression method of Greenwald et al. (1995), we regressed the discrimination performance in the test of awareness [(hits + correct rejections) − (false alarms + misses)] onto the rate of fit responses given to episodically related (experimental condition) minus unrelated (control condition) test words. The y-axis intercept was significantly greater than zero. This indicates that the integration of events across consciousness levels was significant, when conscious discrimination performance was zero.

of integration, we presented a word from the unconscious event besides a word from the corresponding conscious event in both the experimental and the control condition. These test words were semantically unrelated. But test words in the experimental condition were episodically related by a word (not present in the test trial) that had been the counterpart of each of the test words drawn from the two encoding events. Test words in the control condition were episodically unrelated. Episodically related versus unrelated test words were more often judged as closely related semantically. It thus appears that episodic associations intruded into judgments of semantic distance leading to more fit responses in the experimental versus the control condition. This effect is known from studies with supraliminal stimulus presentations: two unrelated words that had been presented in the same encoding context and were episodically (but not semantically) related, appeared closer semantically than words that had not been presented in the same encoding context; or they appeared equally close as words that were related semantically (McKoon and Ratcliff, 1979, 1986; Dosher and Rosedale, 1991; Patterson et al., 2009; Coane and Balota, 2011). This line of research suggests that connections between mental representations or between nods in the semantic network, which have been co-activated in the same encoding context, acquire a greater linkage strength leading to the impression of stronger conceptual relatedness. The co-occurrence of concepts in naturalistic events is indeed one way how the semantic system may be dynamically (re)organized throughout life (Coane and Balota, 2011). Although test words in the present experimental condition had not occurred in the same encoding context but in two different encoding contexts, they were linked by a third word that was presented in both encoding contexts. This mediated linkage between test words had apparently sufficed to decrease the perceived semantic distance between test words. Remarkably, this was possible with one of the two events processed outside consciousness.

Do these modifications in participants' semantic systems result from plastic chances in the neocortex alone or from additional plastic changes in the medial temporal lobe, particularly the hippocampus? The hippocampus is ordinarily assisting the rapid encoding of events by association formation between co-activated areas of the neocortex (Teyler and DiScenna, 1986; Treves and Rolls, 1994). Our task structure and results speak to a hippocampal role because encoding was rapid (one-trial) and memory representations must have been compositional and flexible (Cohen and Eichenbaum, 1993; Henke, 2010). There was no neuroimaging in the present study but earlier neuroimaging studies give a clue. Reber et al. (2012) used a similar design but presented all encoding events subliminally. There was hippocampal activation during the unconscious encoding of overlapping events and during judgments of semantic distance made on episodically related word pairs presented at test. Moreover, hippocampal activity measured during the encoding of overlapping subliminal events predicted judgments of semantic distance at test. The hippocampus was also activated in studies using supraliminal stimuli, either at the time when overlapping events were encoded or when inferences were made at test (Heckers et al., 2004; Preston et al., 2004; Greene et al., 2006; Shohamy and Wagner, 2008; Zeithamova and Preston, 2010; Zeithamova et al., 2012). Because the hippocampus played a role both in studies of inference that used supraliminal encoding events and in a study that used subliminal encoding events, we assume that the hippocampus is also engaged when encoding events were both conscious and unconscious. Increasing evidence suggests that the hippocampus engages in all tasks that require the rapid encoding of new, compositional, and flexible associations irrespective of the level of consciousness of stimulus processing (Henke, 2010).

The absence of an effect of time/stimuli between two overlapping encoding events on test performance replicates our previous result of the successful integration of two discrete subliminal events, which was also unaffected by intervening time/stimuli (Reber and Henke, 2012). The lack of a temporal distance effect in these two experiments is intriguing given previous evidence that temporal contiguity influences the retrieval from episodic memory (Temporal Context Model; Howard and Kahana, 1999; Howard et al., 2005). Core assumptions of the Temporal Context Model entail context-representations that change gradually over time and that act as retrieval cues for the items learned in the same contexts. Because items that are learned in close temporal proximity have similar contexts, they are more likely to be recalled (Howard and Kahana, 1999). If an encoding item is shown twice to boost learning, the context of its second presentation will resemble the context of its first presentation due to its presence at both moments in time. In our study, B words must have induced contiguity between the two overlapping encoding events A–B and B–C. The presence of B words in both encoding events may have rendered the two events more independent of their temporal (dis)contiguity (Howard et al., 2005). In other words, the configurational contiguity induced by the presence of B words in both overlapping events may have anchored and linked the two events to the extent of neutralizing potential adverse effects of temporal discontiguity (and interfering information) presented between overlapping events (Howard et al., 2005).

The current design does not allow pinning down the time point at which the integration of conscious and unconscious memories took place – at encoding or test. Either way, representations of unconscious events must have been solid and stable over time because test performance was not modulated by whether the unconscious event was preceding or following the corresponding conscious event. Hence, conscious and unconscious memory traces could be integrated independently of the order, in which the memory traces were formed. If integration of memory traces occurred at test, it may have been advantageous to encode the conscious event first because consciously acquired memories are stronger and decay not as rapidly as unconsciously acquired memories; after all, the time interval between the first event and the final test was as long as 170 s. Under the assumption that memories are integrated at retrieval, the lack of an order effect means that conscious and unconscious memories outlasted this time period equally well. If participants integrated memories already when the second encoding event was presented, the first memory trace had to outlast 7–72 s, which was certainly the case for both unconscious and conscious memories. The absence of an order effect additionally suggests that it was not easier to link an unconscious (weak) representation to a pre-existing conscious (strong) representation

than vice versa. Hence, for these time intervals, the lack of an order effect suggests that unconscious memories were on a par with conscious memories regarding their endurance and flexibility.

We had hypothesized that conscious and unconscious memory representations could be integrated into a cohesive memory space assuming that the same memory system supports the encoding of subliminal and supraliminal events (Henke et al., 2003; Degonda et al., 2005; Reber et al., 2012). Yet, such harmonious interactions between explicit and implicit memory may not have been expected given past evidence of dissociations and competing interactions between implicit and explicit memory (Wagner et al., 2000; Poldrack et al., 2001). Such adverse interactions concerned separate memory systems (hippocampal interactions with other structures) that competed in the process of learning the same kind of material or procedure. Our study, however, concerned the encoding of distinct events by the same memory system that works at two different levels of intensity – conscious and unconscious. Furthermore, the information acquired in the first and the second overlapping event was neither identical nor conflicting (as in Degonda et al., 2005) but additive, which may have contributed to the smooth integration of information across consciousness levels.

Given that events can be encoded with and without consciousness by way of the hippocampus and related cortices (Henke et al., 2003; Degonda et al., 2005; Henke, 2010; Reber et al., 2012), the organization of consciously and unconsciously acquired information into a single, cohesive hippocampal memory space appears more economic than the organization of information in two discrete hippocampal memory spaces divided by consciousness. Linked episodic knowledge – conscious or unconscious – informs and guides us better through life than episodic knowledge segmented into levels of representation. Moreover, the level of representation of episodic knowledge is dynamic and shifts over time. A single hippocampal memory space maintains the stability and coherence of its organization when episodic memories shift from unconscious to conscious (Fischer et al., 2006; Drosopoulos et al., 2011; Yordanova et al., 2012) or from conscious to unconscious in the course of consolidation (Saletin et al., 2011).

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REFERENCES

Coane, J. H., and Balota, D. A. (2011). Face (and nose) priming for book: the malleability of semantic memory. *Exp. Psychol.* 58, 62–70. doi:10.1027/1618-3169/a000068

Cohen, N. J., and Eichenbaum, H. (1993). *Memory, Amnesia, and the Hippocampal System*. Cambridge, MA: MIT Press.

Degonda, N., Mondadori, C. R. A., Bosshardt, S., Schmidt, C. F., Boesiger, P., Nitsch, R. M., et al. (2005). Implicit associative learning engages the hippocampus and interacts with explicit associative learning. *Neuron* 46, 505–520. doi:10.1016/j.neuron.2005.02.030

Dosher, B. A., and Rosedale, G. (1991). Judgments of semantic and episodic relatedness-common time-course and failure of segregation. *J. Mem. Lang.* 30, 125–160. doi:10.1016/0749-596X(91)90001-Z

Drosopoulos, S., Harrer, D., and Born, J. (2011). Sleep and awareness about presence of regularity speed the transition from implicit to explicit knowledge. *Biol. Psychol.* 86, 168–173. doi:10.1016/j.biopsycho.2010.11.005

Duss, S. B., Oggier, S., Reber, T. P., and Henke, K. (2011). Formation of semantic associations between subliminally presented face-word pairs. *Conscious. Cogn.* 20, 928–935. doi:10.1016/j.concog.2011.03.018

Fischer, S., Drosopoulos, S., Tsen, J., and Born, J. (2006). Implicit learning – explicit knowing: a role for sleep in memory system interaction. *J. Cogn. Neurosci.* 18, 311–319. doi:10.1162/jocn.2006.18.3.311

Greene, A. J., Gross, W. L., Elsinger, C. L., and Rao, S. M. (2006). An FMRI analysis of the human hippocampus: inference, context, and task awareness. *J. Cogn. Neurosci.* 18, 1156–1173. doi:10.1162/jocn.2006.18.7.1156

Greene, A. J., Spellman, B. A., Dusek, J. A., Eichenbaum, H. B., and Levy, W. B. (2001). Relational learning with and without awareness: transitive inference using nonverbal stimuli in humans. *Mem. Cogn.* 29, 893–902. doi:10.3758/BF03196418

Greenwald, A. G., Klinger, M. R., and Schuh, E. S. (1995). Activation by marginally perceptible ("subliminal") stimuli: dissociation of unconscious from conscious cognition. *J. Exp. Psychol. Gen.* 124, 22–42. doi:10.1037/0096-3445.124.1.22

Heckers, S., Zalesak, M., Weiss, A. P., Ditman, T., and Titone, D. (2004). Hippocampal activation during transitive inference in humans. *Hippocampus* 14, 153–162. doi:10.1002/hipo.10189

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nat. Rev. Neurosci.* 11, 523–532. doi:10.1038/nrn2850

Henke, K., Treyer, V., Nagy, E. T., Kneifel, S., Dürsteler, M., Nitsch, R. M., et al. (2003). Active hippocampus during nonconscious memories. *Conscious. Cogn.* 12, 31–48. doi:10.1016/S1053-8100(02)00006-5

Howard, M. W., Fotedar, M. S., Datey, A. V., and Hasselmo, M. E. (2005). The temporal context model in spatial navigation and relational learning: toward a common explanation of medial temporal lobe function across domains. *Psychol. Rev.* 112, 75–116. doi:10.1037/0033-295X.112.1.75

Howard, M. W., and Kahana, M. J. (1999). Contextual variability and serial position effects in free recall. *J. Exp. Psychol. Learn. Mem. Cogn.* 25, 923–941. doi:10.1037/0278-7393.25.4.923

Leo, P. D., and Greene, A. J. (2008). Is awareness necessary for true inference? *Mem. Cogn.* 36, 1079–1086. doi:10.3758/MC.36.6.1079

McKoon, G., and Ratcliff, R. (1979). Priming in episodic and semantic memory. *J. Verbal Learning Verbal Behav.* 18, 463–480. doi:10.1016/S0022-5371(79)90255-X

McKoon, G., and Ratcliff, R. (1986). Automatic activation of episodic information in a semantic memory task. *J. Exp. Psychol. Learn. Mem. Cogn.* 12, 108–115. doi:10.1037/0278-7393.12.1.108

Moses, S. N., Brown, T. M., Ryan, J. D., and McIntosh, A. R. (2010). Neural system interactions underlying human transitive inference. *Hippocampus* 20, 894–901. doi:10.1002/hipo.20735

Patterson, M. M., Light, L. L., Van Ocker, J. C., and Olfman, D. (2009). Discriminating semantic from episodic relatedness in young and older adults. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 16, 535–562. doi:10.1080/13825580902866638

Poldrack, R. A., Clark, J., Paré-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., et al. (2001). Interactive memory systems in the human brain. *Nature* 414, 546–550. doi:10.1038/35107080

Preston, A. R., Shrager, Y., Dudukovic, N. M., and Gabrieli, J. D. (2004). Hippocampal contribution to the novel use of relational information in declarative memory. *Hippocampus* 14, 148–152. doi:10.1002/hipo.20009

Reber, T. P., and Henke, K. (2011). Rapid formation and flexible expression of memories of subliminal word pairs. *Front. Psychol.* 2:343. doi:10.3389/fpsyg.2011.00343

Reber, T. P., and Henke, K. (2012). Integrating unseen events over time. *Conscious. Cogn.* 21, 953–960. doi:10.1016/j.concog.2012.02.013

Reber, T. P., Luechinger, R., Boesiger, P., and Henke, K. (2012). Unconscious relational inference recruits the hippocampus. *J. Neurosci.* 32, 6138–6148. doi:10.1523/JNEUROSCI.5639-11.2012

Reingold, E. M., and Merikle, P. M. (1988). Using direct and indirect measures to study perception without awareness. *Percept. Psychophys.* 44, 563–575. doi:10.3758/BF03207490

Saletin, J. M., Goldstein, A. N., and Walker, M. P. (2011). The role of sleep in directed forgetting and remembering of human memories. *Cereb. Cortex* 21, 2534–2541. doi:10.1093/cercor/bhr034

Shohamy, D., and Wagner, A. D. (2008). Integrating memories in the human brain: hippocampal-midbrain encoding of overlapping events. *Neuron* 60, 378–389. doi:10.1016/j.neuron.2008.09.023

Smith, C., and Squire, L. R. (2005). Declarative memory, awareness, and transitive inference. *J. Neurosci.* 25, 10138–10146. doi:10.1523/JNEUROSCI.2731-05.2005

Snodgrass, M., and Shevrin, H. (2006). Unconscious inhibition and facilitation at the objective detection threshold: replicable and qualitatively different unconscious perceptual effects. *Cognition* 101, 43–79. doi:10.1016/j.cognition.2005.06.006

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiol. Learn. Mem.* 82, 171–177. doi:10.1016/j.nlm.2004.06.005

Teyler, T. J., and DiScenna, P. (1986). The hippocampus memory indexing theory. *Behav. Neurosci.* 100, 147–154. doi:10.1037/0735-7044.100.2.147

Treves, A., and Rolls, E. T. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus* 4, 374–391. doi:10.1002/hipo.450040319

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Voermans, N. C., Petersson, K. M., Daudey, L., Weber, B., Van Spaendonck, K. P., Kremer, H. P., et al. (2004). Interaction between the human hippocampus and the caudate nucleus during route recognition. *Neuron* 43, 427–435. doi:10.1016/j.neuron.2004.07.009

Wagner, A. D., Maril, A., and Schacter, D. L. (2000). Interactions between forms of memory: when priming hinders new episodic learning. *J. Cogn. Neurosci.* 12(Suppl. 2), 52–60. doi:10.1162/089892900564064

Yordanova, J., Kolev, V., Wagner, U., Born, J., and Verleger, R. (2012). Increased alpha (8-12 Hz) activity during slow wave sleep as a marker for the transition from implicit knowledge to explicit insight. *J. Cogn. Neurosci.* 24, 119–132. doi:10.1162/jocn_a_00097

Zeithamova, D., Dominick, A. L., and Preston, A. R. (2012). Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. *Neuron* 75, 168–179. doi:10.1016/j.neuron.2012.05.010

Zeithamova, D., and Preston, A. R. (2010). Flexible memories: differential roles for medial temporal lobe and prefrontal cortex in cross-episode binding. *J. Neurosci.* 30, 14676–14684. doi:10.1523/JNEUROSCI.3250-10.2010

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Detecting analogies unconsciously

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Analogies may arise from the conscious detection of similarities between a present and a past situation. In this functional magnetic resonance imaging study, we tested whether young volunteers would detect analogies unconsciously between a current supraliminal (visible) and a past subliminal (invisible) situation. The subliminal encoding of the past situation precludes awareness of analogy detection in the current situation. First, participants encoded subliminal pairs of unrelated words in either one or nine encoding trials. Later, they judged the semantic fit of supraliminally presented new words that either retained a previously encoded semantic relation ("analog") or not ("broken analog"). Words in analogs versus broken analogs were judged closer semantically, which indicates unconscious analogy detection. Hippocampal activity associated with subliminal encoding correlated with the behavioral measure of unconscious analogy detection. Analogs versus broken analogs were processed with reduced prefrontal but enhanced medial temporal activity. We conclude that analogous episodes can be detected even unconsciously drawing on the episodic memory network.

Keywords: episodic memory, subliminal, analogical mapping, consciousness, flexibility, hippocampus, medial temporal lobe

INTRODUCTION

We pull up analogies to make inventions, solve problems, and plan and adapt our behavior in new situations. The detection of analogies assumes a source situation that is remembered and a present situation that is interpreted in light of the source situation (Gentner, 1983). For example, bodily and facial cues of a young couple flirting might suddenly remind us of an episode at a scientific session where two scientists eager for collaboration made their first contact. Analogies arise from the detection of correspondences or *mappings* between elements in a current situation and elements in a memory representation of a past situation. The detection of situational analogies depends on a flexible expression of source memories because the format and elements of the source situation often differ from the format and elements of a current situation. Flexibility of memory expression is considered a hallmark of episodic memory (Cohen and Eichenbaum, 1993; Frank et al., 2003; Henke, 2010).

Analogies often spring to mind suddenly and unexpectedly. The detection of analogies likely transcends an unconscious stage before entering consciousness. The source knowledge is usually stored in either episodic (Gentner et al., 1993; Schunn and Dunbar, 1996; Wharton et al., 1996; Day and Goldstone, 2011) or semantic memory (Spellman et al., 2001; Bunge et al., 2005; Green et al., 2006a,b, 2010) with both forms of memory hypothesized to be associated with consciousness of encoding/retrieval (Squire and Zola, 1996; Moscovitch, 2008). Episodic memory depends on hippocampal processing (Cohen and Eichenbaum, 1993; Reber and Squire, 1994; Squire and Zola, 1996; Squire et al., 2007; Moscovitch, 2008) and hippocampal activity closely tracks conscious experience (Kreiman et al., 2002; Quiroga et al., 2008). A prominent role in analogical mapping has been assigned to the prefrontal cortex (Morrison et al., 2004; Bunge et al., 2005; Green et al., 2006b, 2010; Speed, 2010; Knowlton et al., 2012), which has also been linked to consciousness of information processing (Dehaene and Naccache, 2001; Dehaene and Changeux, 2011). Hence, the detection of analogies in a current situation may require the conscious retrieval of a source situation.

We hypothesize that the detection of analogies between a source and a current situation does not strictly require conscious awareness of encoding/retrieving. On the contrary, we assume that analogical mapping proceeds automatically and unconsciously as a consequence of a facilitated processing of relations between elements in a current situation based on the past experience of similar relations (Schunn and Dunbar, 1996; Leech et al., 2008). Then, unconscious analogical mapping may or may not emerge to consciousness. Evidence for unconscious analogical mapping comes from purely behavioral studies that assessed awareness of analogical mapping with *post hoc* self-reports (Schunn and Dunbar, 1996; Silberman et al., 2005; Green et al., 2006a; Day and Gentner, 2007; Day and Goldstone, 2011). A more stringent way to test for unconscious analogical mapping is by presenting the source situation subliminally (invisibly) for unconscious encoding. Using subliminal presentations and functional magnetic resonance imaging (fMRI), we gained evidence that unconscious analogy detection is feasible by the way of episodic memory network including hippocampus.

MATERIALS AND METHODS

OVERVIEW

For subliminal encoding, we presented pairs of unrelated words (e.g., table–car) to establish novel unconscious source knowledge (**Figure 1**). Participants performed an attention task during

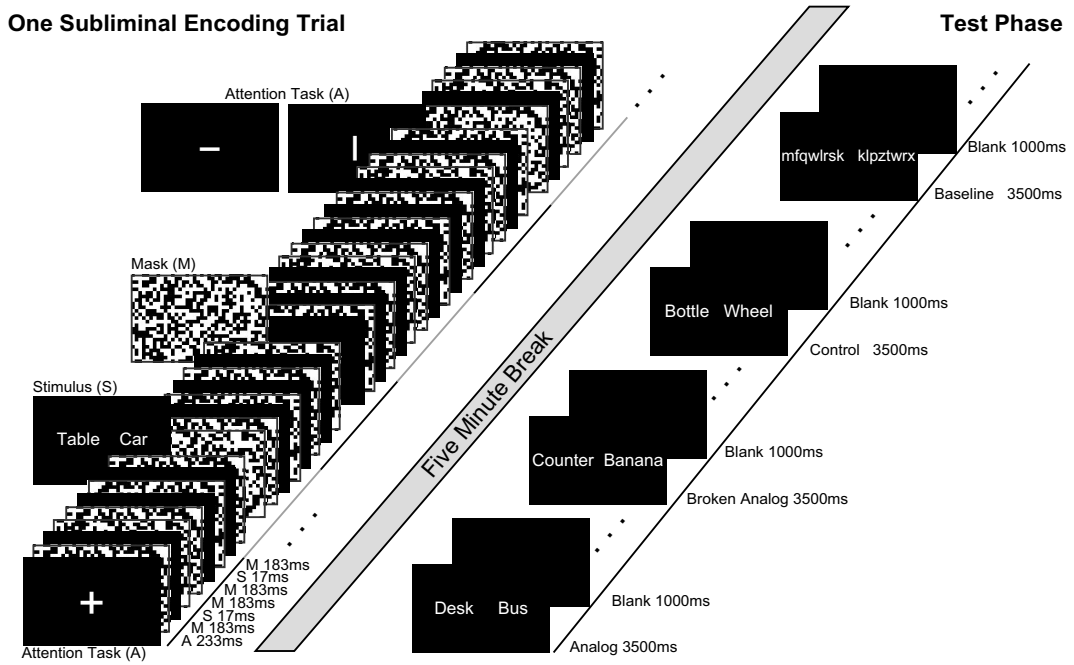


FIGURE 1 | Subliminal and supraliminal trials. Left side, subliminal word pairs were presented for 17 ms between pattern masks. Participants were not informed of subliminal stimuli; they performed an attention task during the subliminal stimulation sequence. There was a break of 5 min between encoding and test. Right side, at test, pairs of new words were presented supraliminal in three conditions for participants to decide whether words in a pair fit together semantically. Words in analogs were new but retained semantic relations from subliminal encoding word pairs (encoding: table–car; test: desk–bus). Semantic relations were broken in Broken Analogs. Control pairs consisted of words that were neither semantically close to encoding words nor retained semantic relations. Successive stimuli are depicted from bottom left to top right.

subliminal encoding to ensure that their attentional focus remained on the stimulus display. After 5 min of quiet rest, we presented word pairs for conscious inspection that consisted of new (not subliminally presented) words that were conceptually related to the subliminal encoding words (**Figure 1**). The conceptual relations that were established during unconscious encoding were either kept intact at test (analogs) or not (broken analogs) (Silberman et al., 2005; Reber and Henke, 2011). Thus, an analogous word pair (e.g., desk–bus) maintained the conceptual relation (e.g., a piece of furniture–a means of transport) that was established during an encoding trial (e.g., table–car). Broken analogs combined words (e.g., counter–banana) that were conceptually related to words from two different encoding trials (e.g., table–car; keyboard–apple). The participants' task was to judge whether the two words in a pair fit together semantically or not (forced-choice test). More fit responses to analogs than broken analogs suggest that novel source knowledge was established and that the mapping of source knowledge onto the target was successful. Crucially, the participants were unaware of any memory reactivation because encoding stimuli were subliminal. Subliminal encoding precluded participants' awareness of analogical relations between encoding and test words. We varied the number of encoding trials between participants to measure potential effects of subliminal overlearning such as semanticization (disengagement of hippocampus over encoding trials) and unitized versus compositional representation of encoding word pairs. To this aim, half of participants ($N = 30$) encoded each subliminal word pair in one subliminal encoding trial, while the other half of participants encoded each subliminal word pair in nine subliminal encoding trials (**Figure 2D**).

PARTICIPANTS

Participants were 60 right-handed men with a mean age of 24.6 years [standard deviation (SD) = 4.6 years]. They reported no current or past neurological or psychiatric illness, were native German speakers, and had normal or corrected-to-normal vision. The study was approved by the local ethics committee.

The analysis of the behavioral data included the datasets of 57 participants. Three participants were excluded because their performance on the attention task (given during subliminal stimulation) was below two SDs of the group mean. SDs were derived separately for the participants in the one-trial encoding condition and participants in the nine-trial encoding condition because mean hit rates on the attention task differed between encoding conditions (see Results).

Performance on the attention task correlated inversely with the quality of encoding subliminal word pairs (see Results). Hence, performance on the attention task could be taken as proxy for subliminal encoding quality. In order to isolate the good from the poor subliminal encoders, we performed a median split on the z-values of the attention task. In the following, we refer to low versus high performers on the attention task as good versus poor subliminal encoders, respectively. Because half of participants encoded word pairs in one and half in the nine subliminal encoding trials, the median split resulted in four subgroups of participants:

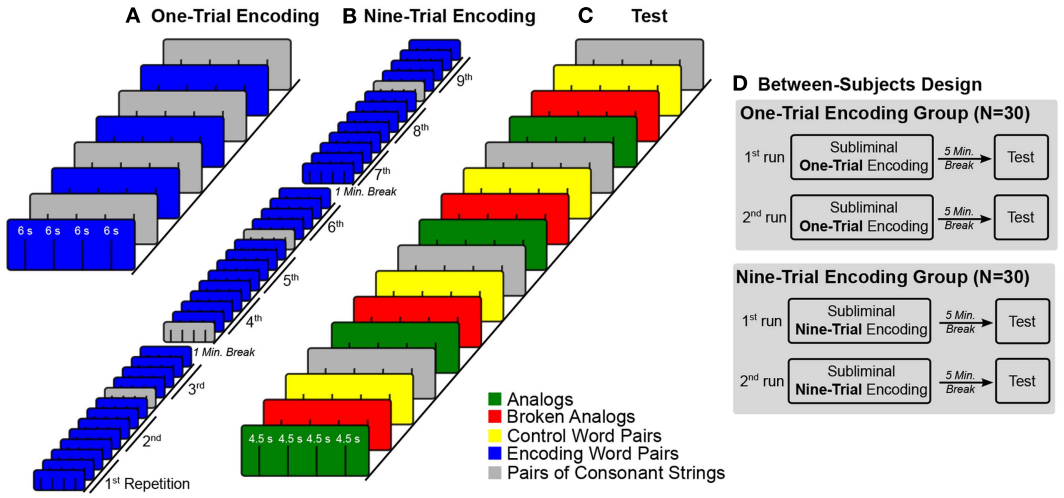


FIGURE 2 | Experimental design. **(A–C)** The colored boxes illustrate trial blocks that belong to a certain experimental condition. Lines within colored boxes stand for individual trials. The sequence of blocks over time is given from bottom left to top right. **(A)** The fMRI time-series for subliminal one-trial encoding entailed four blocks of four subliminal word pairs each and four blocks of four pairs of consonant strings each. Blocks of word pairs (blue) alternated with blocks of pairs of consonant strings (gray). **(B)** In the fMRI time-series for subliminal nine-trial encoding, the four blocks with word pairs were repeated nine times for a better encoding. Blocks with pairs of consonant strings were not repeated. These blocks were interspersed at pseudo-random positions in the time-series. **(C)** The test fMRI time-series embraced four conditions of four blocks each. Each block contained four trials. Condition blocks were presented in a fixed alternating sequence. **(D)** Half of participants were assigned to the one-trial encoding group and the other half to the nine-trial encoding group. Both groups took two experimental runs. Each run consisted of an encoding part, a 5-min encoding-test interval, and a test part.

of 29 poor subliminal encoders, 15 were in the one-trial encoding condition and 14 in the nine-trial encoding condition; of 28 good subliminal encoders, 13 were in the one-trial encoding condition and 15 in the nine-trial encoding condition.

The analysis of functional imaging data included 51 participants as the data of nine participants were excluded because of the excessive scan-to-scan movements ($N = 1$), slice-artifacts ($N = 5$), and – as mentioned above – very low performance on the attention task ($N = 3$). Of the 51 evaluated fMRI datasets, 27 corresponded to poor subliminal encoders, of whom 14 belonged to the one-trial encoding condition and 13 to the nine-trial encoding condition. Twenty-four datasets corresponded to good subliminal encoders, of whom 12 were in the one-trial encoding condition and 12 in the nine-trial encoding condition.

APPARATUS

The experiment took place in a magnetic resonance imaging (MRI) chamber that was darkened by turning off all lights and by a black curtain that prevented light from entering the MRI chamber. A BenQ SP831 DLP projector was placed in between the curtain and the shielding glass to project the stimulus sequence onto a screen positioned in front of the MR scanner. Stimuli spanned a visual field of 11°(height) × 13 (width). They were back-projected onto the screen. Participants viewed the stimuli through two mirrors mounted on the head-coil. The stimulus sequence was generated by a laptop running the software Presentation[1]. The visual display had a resolution of 1024 × 768 pixel and was presented with a refresh rate of 60 Hz.

SUBLIMINAL PRESENTATION PROTOCOL

One subliminal encoding trial entailed 12 presentations of a word pair (W) within a 6-s time-window (Degonda et al., 2005) (**Figure 1**). Each of the 12 presentations lasted 17 ms and was preceded and followed by random-dot pattern masks (M; masking stimuli) that were presented for 183 ms each. Preceding two such masked presentations of a word pair (M W M M W M), either a fixation cross, a horizontal, or a vertical bar (A) was presented for 233 ms. This presentation sequence (A M W M M W M) lasted 1 s and was repeated six times with the same word pair as subliminal stimulus. The fixation cross was presented randomly five in six times; a horizontal or vertical bar was presented with equal probability once in six times. The participants' task was to focus gaze on the fixation cross/bar and to indicate the orientation of a bar by button press immediately upon the bar's occurrence.

PRACTICE RUN

The practice run allowed for the conscious inspection of both encoding and test word pairs. We wanted participants to note the correspondence between encoding and test word pairs, which should allow them to install a task-set for the ensuing subliminal trials. Task-sets may guide the processing of subliminal stimuli (Kiefer and Martens, 2010; Reber and Henke, 2011). The encoding part of the practice run took 2.4 min. It was followed by 5 min of rest. The practice run ended with the test part, which took 4.8 min. Encoding and test word pairs were presented once for 3.5 s with inter-stimulus intervals of 1 s. Participants engaged in the same

[1]http://www.neurobs.com/presentation

forced-choice task during encoding and test. The forced-choice task required them to decide whether the two words in an encoding or test pair fit together semantically or not. Since words in all pairs were semantically distant, we asked participants to relax their response criterion in order to give an approximately equal amount of fit and don't fit responses. When pairs of consonant strings (baseline) were presented, participants were asked to judge the visual fit between two consonant strings as if they were two art sculptures. This instruction was chosen to foster a holistic processing of consonant strings, which makes the processing comparable to the equally holistic processing of words in pairs.

After the completion of this supraliminal practice run, participants were interviewed on whether they had noticed the correspondence between encoding word pairs and analogs. If they could name at least one encoding word pair and its analog (e.g., table–car; desk–bus), they were classified as having gained insight into the task structure. In a previous study (Reber and Henke, 2011), participants with versus without insight performed better in the following subliminal encoding and retrieval task. This finding was not replicated in the present study. Twenty-eight participants gained insight into the task structure during the practice run. The difference in the baseline-corrected percentage of fit responses given to analogs versus broken analogs in the main experiment did not differ between participants, who gained insight ($M = 2.4\%$, $SD = 1.2\%$, $N = 28$), and participants, who failed to gain insight ($M = 0.5\%$, $SD = 1.1\%$, $N = 29$), $t(55) = 0.625$, $p = 0.534$.

MAIN EXPERIMENT

The main experiment consisted of two experimental runs. Each experimental run started with the encoding part, included a 5-min break and ended with the test part. Unlike the practice run, encoding word pairs were presented subliminally for unconscious encoding (**Figure 1**). The task at test was again a forced-choice judgment of the semantic fit between the two supraliminal words in a test pair, as in the practice run.

For half of the participants, encoding word pairs were presented in one subliminal encoding trial (one-trial encoding) during both experimental runs. Encoding and test word pairs were presented in blocks of four with four blocks per condition (**Figure 2A**). Blocks of encoding word pairs alternated with blocks of pairs of consonant strings (baseline). Half of the encoding time-series started with a block of word pairs and half with a block of pairs of consonant strings. There was a 5-min break between the encoding and test fMRI time-series. In the test fMRI time-series, the order of condition blocks (conditions: analogs, broken analogs, control word pairs, and pairs of consonant strings) was varied between participants according to a Latin-square (**Figure 2C**). The fMRI time-series on subliminal one-trial encoding took 3.2 min and the test fMRI time-series took 4.8 min.

For the other half of participants, each encoding word pair was presented in nine temporally dispersed encoding trials (nine-trial encoding) in both experimental runs (**Figure 2B**). To alleviate tiring, nine-trial encoding was split into three encoding fMRI time-series per experimental run, separated by 1 min breaks, during which time no fMRI data were acquired. The ninefold repetition concerned only word pairs presented in the experimental condition but not the pairs of consonant strings presented in the baseline condition – these were shown only once. The four condition blocks that contained pairs of consonant strings were pseudo-randomly intermixed with the condition blocks that contained word pairs. Before any block of word pairs was repeated, we presented the complete set of encoding word pairs. At test, the order of condition blocks (conditions: analogs, broken analogs, control word pairs, and pairs of consonant strings) was varied between participants according to a Latin-square (**Figure 2C**). The three fMRI time-series on subliminal encoding over nine-trials lasted 16 min in total (5.3 min per times-series; no scanning during the 1-min breaks between time-series). The test fMRI time-series took 4.8 min.

AWARENESS TEST

After the main experiment, participants were asked whether they had noticed words or perceptual fragments thereof during subliminal encoding. Then, participants were informed of the masked presentation of subliminal stimuli. Finally, we conducted an awareness test to measure participants' ability to discriminate masked words. This awareness test consisted of 30 encoding-test trials. On each trial, a word was presented in one subliminal encoding trial with the masking technique of the main experiment. Immediately following the subliminal presentation of a word, we presented two supraliminal words side-by-side for participants to do a forced-choice task. Participants chose which word was semantically related to the preceding subliminal word. The target word was semantically related to the subliminal word and the distracter word was unrelated. The side of the target/distracter was randomized.

STIMULI

We assembled 192 triplets of words that consisted of subordinates to the same concept (e.g., table–desk–counter; car–bus–truck; apple–pear–banana). These triplets were assigned to six lists each containing 32 triplets. Two lists were assigned to the practice run, two lists to the first experimental run, and two lists to the second experimental run. For each run, one list was used to create encoding word pairs, analogs, and broken analogs. The other list was used to create the control word pairs presented at test only. Encoding word pairs were formed by combining the first words of two different triplets (e.g., table–car). Analogs were formed by combining the second words of these triplets (e.g., desk–bus) and broken analogs by combining the third words of two triplets (e.g., counter–banana). Control word pairs were constructed by combining the first, the second, or the third words in two triplets. Furthermore, pairs of randomly generated consonant strings (e.g., cvmgwpls–pklwqvcn; eight different consonants per string) were presented in the encoding and test time-series as a baseline condition. A stimulus list entailed 16 pairs of words or consonant strings (conditions of the encoding fMRI time-series: encoding word pairs, pairs of consonant strings; conditions of the retrieval fMRI time-series: analogs, broken analogs, control word pairs, and pairs of consonant strings).

To counterbalance word pairs between the analogs and broken analogs condition, encoding word pairs were re-arranged (e.g., original list: table–car; counterbalanced list: table–apple). The resulting analogs (counter–pear) and broken analogs (desk–bus) were thus identical to broken analogs and analogs, respectively, in

the initial arrangement. The assignment of the six lists of triplets to conditions and experimental runs was balanced between participants. A further list of stimuli was used for the test of awareness, which was conducted after the main experiment. For the test of awareness, we compiled 60 pairs of conceptually related words. Two pairs (four words) were assigned to one-trial in the awareness test. The word used for subliminal presentation was randomly chosen from the four words. The semantically related word was the target and the distracter word was randomly chosen from the two remaining words.

MAGNETIC RESONANCE IMAGING

The experiment was conducted on a 1.5-T Philips whole-body MRI scanner. We used an eight-channel head coil. fMRI data were obtained with a sensitivity-encoded single-shot echo planar imaging sequence with an acceleration factor $r = 2.0$ (Schmidt et al., 2005). Thirty-four slices along the AC–PC line were acquired without inter-slice gaps. The time of repetition (TR) was 3 s, echo-time (TE) 50 ms, flip-angle $\theta = 90°$. The field of view was 22 cm × 22 cm. The measured voxel-size was 2.75 mm × 2.75 mm × 4 mm, which was reconstructed to a voxel-size of 1.72 mm × 1.72 mm × 4 mm. A standard 3D T1 image was acquired as anatomical reference (TE = 3.8 ms, TR = 8.2 ms, flip-angle $\theta = 8°$, 160 slices, original voxel-size = 1 mm × 1 mm × 1 mm, no interpolation, field of view = 24 cm × 24 cm, no inter-slice gaps).

ANALYSIS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA

The fMRI data were analyzed using the statistical parametric mapping toolbox[2] (SPM 8). Preprocessing included spatial realignment of the EPI images, normalization of EPI images to a standard anatomical space (mean image of 152 subjects from the Montreal Neurological Institute), and spatial smoothing with an 8-mm Gaussian kernel.

fMRI scanning was halted during the breaks between encoding and test.

First-level models were estimated separately for encoding and test. These models included regressors that were created by convolving a canonical hemodynamic response function with box-car functions of the on- and off-sets of the experimental conditions, and six movement-regressors that were estimated during spatial realignment. First-level contrast images of interest (e.g., pairs of words > pairs of consonant strings) were subjected to random effects analyses. Random effects analyses were thresholded at $p = 0.001$ (uncorrected), and the minimum cluster extent was set to 20 consecutive voxels. We adopted a looser statistical threshold ($p = 0.005$, no cluster extent) for the medial and anterior temporal lobe because these regions are of particular interest in the current study.

We needed to compute separate models for one-trial and nine-trial encoding because the encoding time-series differed (**Figure 2**). Hence, we computed separate second-level analyses for one-trial and nine-trial encoding. Based on the behavioral data, we split participants into good and poor subliminal encoders. The second-level analyses therefore included the between-subjects factor Encoding Quality (good versus poor subliminal encoders). The contrast of one-trial encoding was pairs of words > pairs of consonant strings including the data of the good subliminal encoders ($N = 12$). The contrast of nine-trial encoding contained beta-weights of the linear increase of the BOLD signal over the nine repetitions of subliminal word pairs including the data of the good subliminal encoders ($N = 12$). To investigate neural activity obtained at test, we computed an ANOVA with the within-subjects factor Test Condition (analogs, broken analogs) and the between-subjects factors Learning Intensity (one-trial encoding, nine-trial encoding) and Encoding Quality (good subliminal encoders, poor subliminal encoders). The dependent measure consisted of the first-level contrast images analogs > control word pairs and broken analogs > control word pairs. The reported analysis is a t-test of analogs versus broken analogs of this ANOVA for the good subliminal encoders. This contrast collapsed data over Learning Intensity because Learning Intensity did not influence behavioral results ($N = 24$).

To investigate brain–behavior correlations, we performed one-sample t-tests of contrasts of interest (e.g., analogs > broken analogs) including the behavioral measure obtained at test as a covariate of interest.

ANALYSIS OF BEHAVIORAL DATA

Reaction times (RTs) of semantic fit responses given at test were z-transformed per participant. Trials with z-values below or above $M \pm 2$ SD were excluded from analysis. Data were aggregated per condition (mean of RTs; sum of fit/don't fit responses). We arrived at the percentage of fit responses by dividing the number of fit responses given in a certain condition (e.g., analogs, broken analogs, control word pairs) by the sum of fit and don't fit responses given in that condition. To control for a subjects' generic propensity to give fit responses, the percentage of fit responses to control word pairs was subtracted from both the percentage of fit responses given to analogs and the percentage of fit responses given to broken analogs. We refer to the resulting numbers as baseline-corrected percentages of fit responses (**Figure 3**).

RESULTS

GOOD PERFORMANCE ON THE ATTENTION TASK

Because nine-trial encoding took longer and was more tiring than one-trial encoding, the rate of correct responses on the attention task was lower in the nine-trial ($M = 80\%$, SD = 2%, $N = 29$) than the one-trial encoding condition ($M = 96\%$, SD = 3%, $N = 28$) [$t(55) = 21.066$, $p < 10^{-27}$]. Still, the rates of correct responses were high enough in both conditions to assume that participants kept attention up throughout the experiment.

DETECTION OF ANALOGIES TO UNCONSCIOUS MEMORIES

We had hypothesized that the unconscious detection of analogies would yield more fit responses to analogs than broken analogs (Reber and Henke, 2011). Surprisingly, no such effect was apparent for the whole sample ($N = 57$). However, performance on the attention task during subliminal encoding predicted whether participants could detect analogies and yielded a larger number of fit responses to analogs versus broken analogs. A poorer performance on the attention task predicted more fit responses to analogs

[2]http://www.fil.ion.ucl.ac.uk/spm/

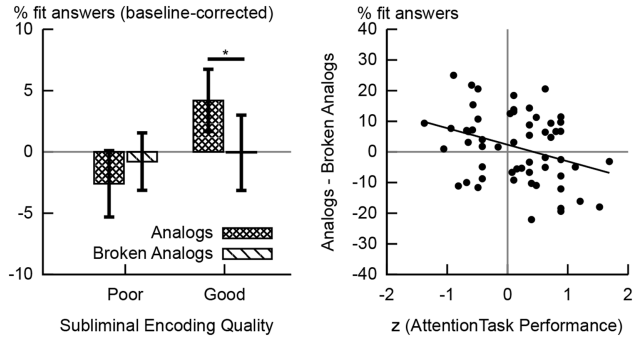


FIGURE 3 | Behavioral results. The left-hand chart shows the percentages of fit responses given to analogs and broken analogs by the group of good and the group of poor subliminal encoders. These percentage values are baseline-corrected; i.e., the percentage of fit responses given to control word pairs was subtracted. Error bars indicate standard errors of means. The difference in the percentage of fit responses to analogs versus broken analogs reached significance at the 5% level in good subliminal encoders. The right-hand chart shows the scatter plot of the correlation between performance on the attention task (during subliminal encoding) and unconscious analogy detection at test (difference in the percentage of fit responses to analogs versus broken analogs). A poorer performance on the attention task predicted a better performance at detecting analogies ($R = -0.332$, $p = 0.012$).

than broken analogs in the whole sample ($R = -0.332$, $p = 0.012$, $N = 57$, **Figure 3**). It thus appears that focusing too much on the attention task took away from the simultaneous processing of subliminal word pairs. We divided our sample by median split into low versus high performers on the attention task or good versus poor subliminal encoders, respectively. Good subliminal encoders gave more fit responses to analogs (baseline-corrected; $M = 4.2\%$, $\mathrm{SD} = 13.5\%$; **Figure 3**) than to broken analogs ($M = -0.6\%$, $\mathrm{SD} = 16.3\%$), $t(27) = 2.432$, $p = 0.022$ (**Figure 3**). No such difference was found for poor subliminal encoders [$M_{\text{analogs}} = -2.6\%$, $\mathrm{SD}_{\text{analogs}} = 14.5\%$, $M_{\text{broken analogs}} = -0.8\%$, $\mathrm{SD}_{\text{broken analogs}} = 12.6\%$, $t(28) = -0.858$, $p = 0.398$; **Figure 3**].

The number of encoding trials did not influence performance at test. The number of fit responses given to analogs versus broken analogs was statistically equal between the one-trial and the nine-trial encoding condition: (a) across the whole group of participants [$t(55) = -0.311$, $p = 0.757$], (b) within the group good subliminal encoders [$t(26) = -0.907$, $p = 0.373$], and (c) within the group of poor subliminal encoders [$t(27) = 0.549$, $p = 0.588$]. This and previous findings (Reber and Henke, 2011) bolster the view that young and healthy participants encode subliminal word pairs equally well in one and nine trials.

PARTICIPANTS WERE UNAWARE OF SUBLIMINAL STIMULI

Interviews conducted after the main experiment revealed that no participant had noticed words or perceptual fragments thereof during subliminal encoding. The test of awareness indicated that participants were unable to discern the subliminal stimuli when directly instructed to do so. The mean frequency of correct responses ($M = 14.98$, $\mathrm{SD} = 2.35$) did not differ from the chance performance (15 correct responses); $t(56) = -0.056$, $p = 0.955$. Neither was there a significant difference in the number of correct responses between the participants in the nine-trial versus the one-trial encoding condition [$M_{9\text{ trial}} = 15.45$, $\mathrm{SD}_{9\text{ trial}} = 2.84$, $M_{1\text{ trial}} = 14.50$, $\mathrm{SD}_{1\text{ trial}} = 1.62$; $t(55) = -1.542$, $p = 0.129$] nor between good versus poor subliminal encoders [$M_{\text{good encoders}} = 15.05$, $\mathrm{SD}_{\text{good encoders}} = 2.40$, $M_{\text{poor encoders}} = 14.93$, $\mathrm{SD}_{\text{poor encoders}} = 2.34$; $t(55) = 0.167$, $p = 0.868$].

UNCONSCIOUS ENCODING OF WORD PAIRS RECRUITS REGIONS OF THE EPISODIC MEMORY NETWORK

Based on previous findings (Henke et al., 2003a,b; Degonda et al., 2005; Reber et al., 2012), we hypothesized that structures of the episodic memory network including the hippocampus would support one-trial encoding of subliminal word pairs. To address this hypothesis, we tested for increases of brain activity during blocks of subliminal word pairs versus blocks of subliminal pairs of consonant strings presented in runs with one encoding trial. We are reporting fMRI results for the good subliminal encoders because only the group of good subliminal encoders showed a successful unconscious detection of analogies as indicated by a larger number of fit responses given to analogs than to broken analogs (**Figure 3**). Significant activity increases were located in two regions within the left hippocampus (**Table 1**). A further cluster of increased activity emerged in the precuneus (BA 7), a region that has been implicated in the mnemonic processing of items with rich contextual details (Gilboa et al., 2004; Cavanna and Trimble, 2006). Further activity increases were located in the posterior cingulate gyrus (BA 31), a constituent of the episodic memory network (Cabeza and Nyberg, 2000), and in the inferior frontal gyrus (BA 46), which has been implicated in the encoding of the relationships between two elements in an associative stimulus (Blumenfeld and Ranganath, 2006; Murray and Ranganath, 2007). Further activity increases targeted BA 6 including the medial frontal gyrus and the precentral gyrus; both regions are thought to support a fluent semantic retrieval (Chee et al., 1999; Binder et al., 2009; Graves et al., 2010; Segaert et al., 2012).

The analyses of nine-trial subliminal encoding corroborate that structures of the episodic memory network subserved the encoding of subliminal word pairs. We assessed effects of a regressor that increased linearly with each repetition of a subliminal word pair (**Table 2**). Good subliminal encoders displayed signal increases over repetitions in the left anterior hippocampus and the right hippocampus extending into right rhinal cortex. Although stimulus repetitions have been reported to be associated with decreasing activity (repetition suppression) in the medial temporal lobe (Turk-Browne et al., 2006; Vannini et al., 2012; Manelis et al., 2013), others report repetition enhancement (Kirwan et al., 2009; Greene and Soto, 2012). A likely reason for the current repetition enhancement is the brief presentation time (17 ms), which is associated with a weak signal. But this weak signal may gain in strength over repetitions, an effect found in a previous study (Müller et al., 2013). A progressively deeper semantic analysis of word pairs was suggested by a linear increase of activity in lateral temporal cortex and prefrontal cortex. Temporal repetition enhancement was located in the bilateral temporal poles and left inferior temporal gyrus suggesting that words were analyzed

Table 1 | Onefold encoding of subliminal word pairs.

Brain region	BA	Left/right	MNI-coordinates			*k*	*t*	*z*
			x	*y*	*z*			
WORD PAIRS > CONSONANT STRINGS								
Inferior frontal gyrus	46	R	40	34	8	21	4.17	3.56
Medial frontal gyrus	6	L/R	0	−10	70	121	4.77	3.94
Precentral gyrus	6	L	−60	−12	40	21	4.62	3.85
Hippocampus		L	−38	−22	−12	55	4.22	3.59
Hippocampus		L	−32	−40	0	59	4.42	3.72
Posterior cingulate gyrus	31	L	−10	−44	46	33	4.93	4.03
Precuneus	7	R	8	−60	44	49	5.03	4.09
CONSONANT STRINGS > WORD PAIRS								
Lingual gyrus, fusiform gyrus	18	L	−22	−78	−6	38	5.00	4.07

N = 12 (good subliminal encoders); statistical maps thresholded at p = 0.005, k = 0 in medial and anterior temporal lobe regions, all other regions p = 0.001, k = 20.

Table 2 | Ninefold encoding of subliminal word pairs.

Brain region	BA	Left/right	MNI-coordinates			*k*	*t*	*z*
			x	*y*	*z*			
LINEAR INCREASE OF BOLD SIGNAL WITH STIMULUS REPETITIONS								
Temporal pole	38	R	38	22	−38	80	5.91	4.53
Temporal pole	38	L	−36	18	−40	37	4.73	3.89
Superior frontal gyrus	6	L	−12	16	68	24	4.41	3.7
Inferior temporal gyrus	20	L	−52	−4	−36	57	6.19	4.66
Putamen		R	26	−12	4	29	4.58	3.8
Hippocampus		L	−28	−14	−24	69	4.36	3.66
Hippocampus, rhinal cortex	35	R	26	−22	−18	27	4.42	3.7
Medial frontal gyrus	6	L/R	8	−28	62	72	5.53	4.33
LINEAR DECREASE OF BOLD SIGNAL WITH STIMULUS REPETITIONS								
Middle occipital gyrus	19	L	−32	−92	26	40	5.46	4.29
Supramarginal gyrus	40	L	−62	−48	32	37	4.79	3.92

N = 12 (good subliminal encoders); statistical maps thresholded at p = 0.005, k = 0 in medial and anterior temporal lobe regions, all other regions p = 0.001, k = 20.

to a high level of abstraction (Patterson et al., 2007). Prefrontal repetition enhancements were located in the medial and superior frontal gyrus (both BA 6), which have been implicated in fluent semantic retrieval (Binder et al., 2009). There were also two regions of repetition suppression, one in left middle occipital gyrus and the other in left supramarginal gyrus likely associated with a facilitated visual analysis of words (Stoeckel et al., 2009).

FACILITATED PROCESSING OF SEMANTIC RELATIONS IN ANALOGS

To assess neural correlates of unconscious analogy detection, we contrasted neural activity of good subliminal encoders between the processing of analogs and broken analogs (collapsed over Learning Intensity) (**Table 3**). Analogs versus broken analogs evoked activity enhancements in the left perirhinal cortex. Large areas in the prefrontal cortex exhibited reduced activity during the processing of analogs versus broken analogs (**Table 3**). We assume that memories of subliminal word pairs were reactivated through the left perirhinal cortex. The perirhinal cortex has been suggested to store within-domain associations such as word–word associations (Mayes et al., 2007). The perirhinal cortex may have triggered the reactivation of neocortical memory traces of word pairs in the regions of prefrontal cortex that support semantic analyses and analogical reasoning (Morrison et al., 2004; Bunge et al., 2005; Green et al., 2006b, 2010). These prefrontal activations were smaller than activations in these same regions evoked in response to broken analogs. The concerned regions were the right middle and superior frontal gyrus (BA 10, 11) and the left middle frontal gyrus (BA 9, 10). These ventromedial prefrontal regions have been found to support the analogical mapping of elements of a current with elements of a past episode (Green et al., 2006b, 2010). Accordingly, unconscious memories of subliminal word pairs in the left rhinal cortex may have facilitated the processing of semantic relations between words in analogs by way of the ventromedial prefrontal cortex. Signal attenuations to analogs versus broken analogs in more lateral prefrontal regions may have

Table 3 | Retrieval of analogous semantic relations.

Brain region	BA	Left/right	MNI-coordinates			*k*	*t*	*z*
			x	*y*	*z*			
ANALOGS > BROKEN ANALOGS								
Perirhinal cortex	35	L	−18	−32	−14	8	3.02	2.94
BROKEN ANALOGS > ANALOGS								
Middle frontal gyrus	10	R	26	56	14	32	3.58	3.45
Superior frontal gyrus	10	R	18	54	28	106	4.27	4.07
Middle frontal gyrus	11	R	24	46	−10	27	4.37	4.15
Medial frontal gyrus	8	L/R	−2	40	46	70	3.94	3.78
Middle frontal gyrus	47	L	−40	38	−4	25	3.67	3.54
Superior frontal gyrus	6	R	14	32	62	24	3.76	3.62
Middle frontal gyrus	9, 46	R	44	30	30	89	4.49	4.26
Middle frontal gyrus	9	L	−34	28	22	106	4.5	4.27
Inferior frontal gyrus	45	L	−48	14	20	62	3.81	3.66
Middle frontal gyrus	6	R	28	12	66	59	4.74	4.47
Middle temporal gyrus	22, 21	R	56	−40	4	236	5.7	5.27
Angular, supramarginal gyrus	39, 40	R	56	−64	36	52	3.87	3.72

N = 24 (good subliminal encoders); statistical maps were thresholded at p = 0.005, k = 0 in medial and anterior temporal lobe regions, all other regions p = 0.001, k = 20.

facilitated the relational analysis of the two words in analogs (Blumenfeld and Ranganath, 2006; Murray and Ranganath, 2007). Further signal attenuations in a more dorsal frontal region (BA 6) suggest that the semantic retrieval was facilitated for words in analogs versus broken analogs (Binder et al., 2009). Other signal attenuations were located in the right angular and supramarginal gyri as well as the right middle and superior temporal gyri. These regions may have facilitated the detection of semantic feature overlap between encoding words (e.g., table–car) and words in analogs (e.g., desk–bus) (Patterson et al., 2007).

Finally, analogs elicited less activation than broken analogs in regions supporting conflict monitoring. These conflict monitoring regions concern posterior portions of the medial prefrontal cortex (Ridderinkhof, 2004), namely the medial frontal gyrus (BA 8) and the middle frontal gyrus (BA 9). These regions in the posterior medial prefrontal cortex may have contributed to the detection of the mismatch between broken analogs and corresponding representations of encoding word pairs.

ENCODING ACTIVATION PREDICTS ANALOGY DETECTION

We correlated the good subliminal encoders' single-trial encoding contrasts (subliminal word pairs versus subliminal pairs of consonant stings) with their behavioral performance on unconscious analogy detection (difference in the percentage of fit responses given to analogs versus broken analogs). Positive correlations appeared in the right hippocampus (**Figure 4**, top), which confirms that the hippocampal encoding of subliminal word pairs mediated analogy detection. Another cluster emerged in the medial frontal gyrus (BA 8) suggesting that increased effort in a region supporting semantic word analysis (Binder et al., 2009) was predictive of better analogy detection at test. A further cluster was located in the superior frontal gyrus (BA 11), which – as noted earlier – has been implicated in the integration of distant semantic concepts (Green et al., 2006b, 2010). A further cluster was located in the left inferior frontal gyrus (BA 47), which has been found to support the evaluation of relationships between elements in a stimulus (Blumenfeld and Ranganath, 2006; Murray and Ranganath, 2007).

Next, we computed correlations between the good subliminal encoders' activity increases over nine encoding trials and their performance at test (**Figure 4**, bottom). A steeper linear activity increase in the left perirhinal cortex predicted a larger number of fit responses to analogs than broken analogs. This result substantiates that the medial temporal lobe subserved the unconscious formation of relational memories. Furthermore, a steeper signal increase in the left temporal pole and the left inferior temporal gyrus predicted a better test performance. This result corroborates that increased neural recruitment in lexical-semantic storage sites during subliminal encoding aided later analogy detection. Finally, a steeper signal increase in the middle cingulate gyrus (BA 24) predicted a better test performance.

BRAIN ACTIVATION AT TEST PREDICTS ANALOGY DETECTION

We correlated the good subliminal encoders' activation difference to analogs versus broken analogs with their performance at detecting analogies unconsciously (**Figure 5**). Positive correlations emerged in the right and left hippocampus and the right thalamus. The thalamus is a part of the episodic memory network (Winocur et al., 1984; Aggleton et al., 2011; Pergola et al., 2012). Our thalamic cluster lies in the mediodorsal nucleus of the thalamus, which has projections to the prefrontal cortex and the temporal lobe (Behrens et al., 2003). Thus, the mediodorsal nucleus of the thalamus might have mediated the interaction of medial temporal with prefrontal regions. Negative correlations were located in the left perirhinal cortex and the right middle temporal gyrus. Activity reductions in perirhinal cortex track familiarity with a stimulus (Voss et al.,

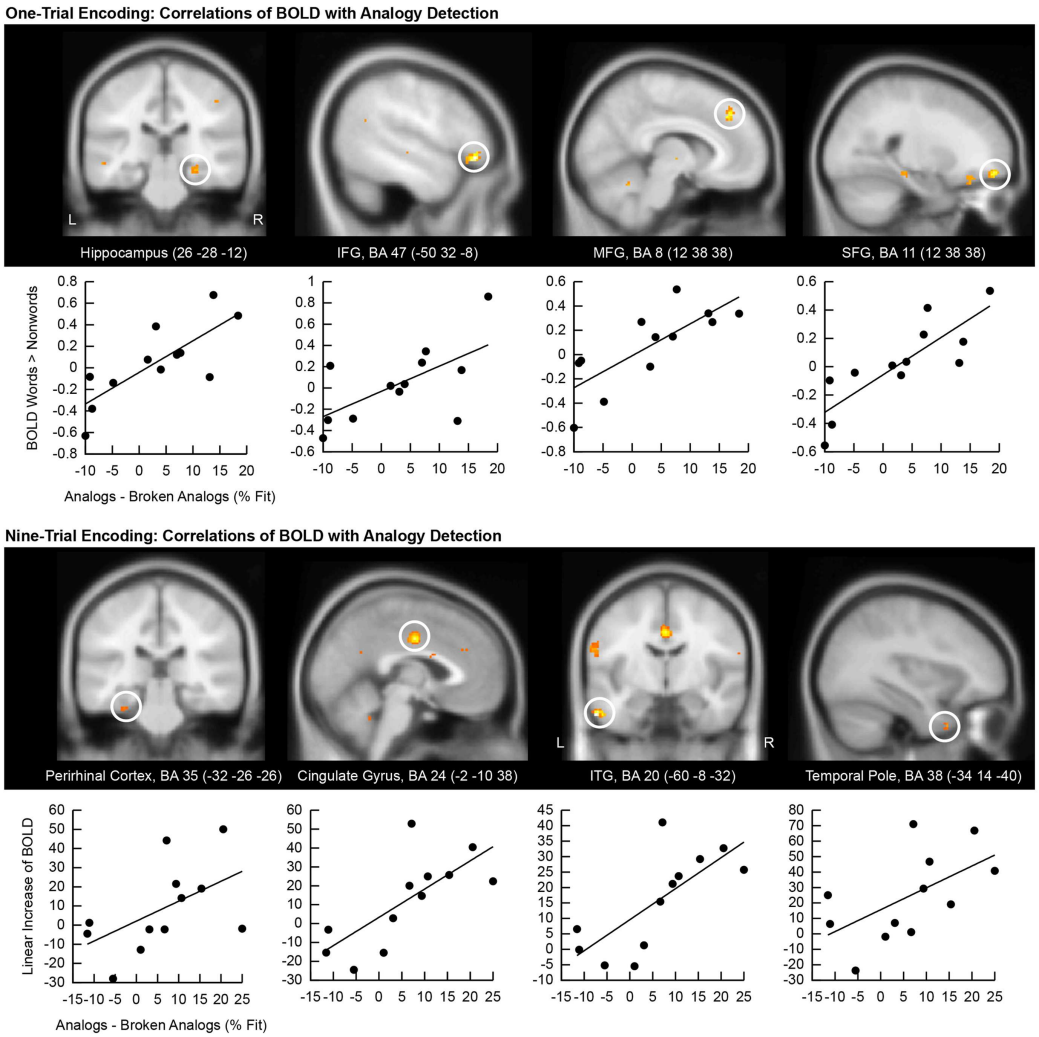


FIGURE 4 | Correlation of encoding-related brain activity with analogy detection at test. The location of the cluster of voxels, where correlations reached significance, is shown on anatomical brain images. BA, Brodmann area; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; MFG, medial frontal gyrus; ITG, inferior temporal gyrus. Scatter plots of these correlations are presented below brain images. The first eigenvariate of the cluster of significantly correlating activity is displayed in arbitrary units on the *y*-axis. The difference in the percentage of fit responses to analogs versus broken analogs is displayed on the *x*-axis. All data come from good subliminal encoders ($N = 12$). The top panel shows correlations of activity increases to subliminal word pairs versus pairs of consonant strings during one-trial encoding with analogy detection. The bottom panel shows correlations of linear activity increases over the ninefold encoding of word pairs with analogy detection.

2009) – in our case the familiarity with semantic relations in analogs. Activity reductions in the middle temporal gyrus likely reflect neural facilitation during the re-processing versus first-time processing of semantic relations. Familiarity and facilitated semantic processing might relate to enhanced analogy detection.

GOOD SUBLIMINAL ENCODERS EXHIBITED MORE ACTIVITY IN THE MEDIAL TEMPORAL LOBE THAN POOR SUBLIMINAL ENCODERS

Comparisons between good and poor subliminal encoders underscored that the episodic memory network supported unconscious memory formation and analogy detection (**Table 4**). A between-group *t*-contrast of good versus poor subliminal encoders' brain activity during one-trial encoding of word pairs revealed two significant left hippocampal clusters. This result indicates that good encoders activated the hippocampus more strongly than poor subliminal encoders in response to subliminal word pairs. Moreover, a steeper increase of the BOLD signal to repeating subliminal word pairs during nine-trial encoding was located in the left hippocampus and bilateral rhinal cortex of good versus poor subliminal encoders. Finally, good subliminal encoders activated the left hippocampus and left parahippocampal gyrus to a greater extent than poor subliminal encoders in response to analogs versus broken analogs presented at test.

DISCUSSION

We report evidence for the unconscious detection of analogical relations in a present and a past situation. Participants encoded subliminal word pairs and later judged the semantic fit of new

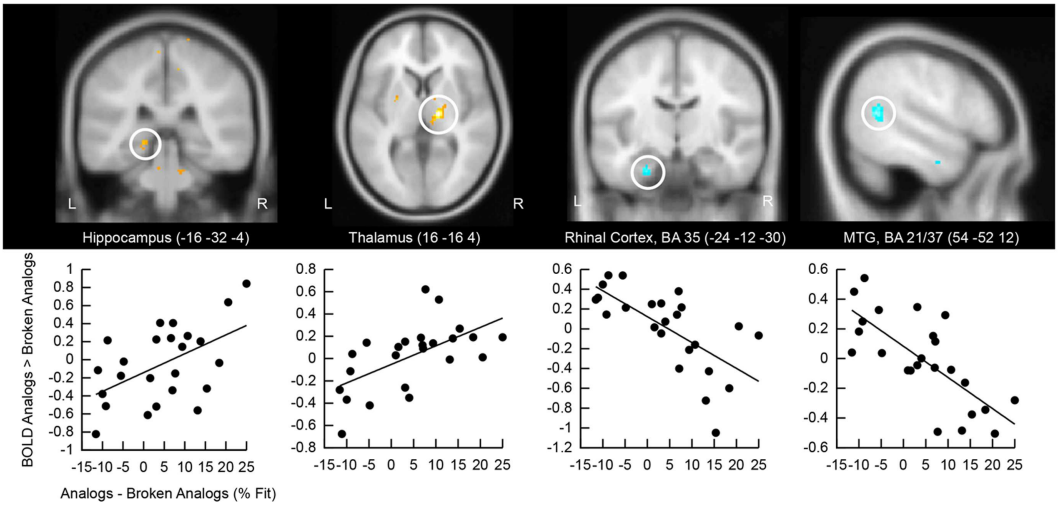


FIGURE 5 | Correlation of retrieval-related brain activity with analogy detection at test. The location of the cluster of voxels, where correlations reached significance, is shown on anatomical brain images. BA, Brodmann area; MTG, middle temporal gyrus. Scatter plots of these correlations are presented below brain images. The first eigenvariate of the cluster of significantly correlating activity is displayed in arbitrary units on the *y*-axis. The difference in the percentage of fit responses to analogs versus broken analogs is displayed on the *x*-axis. All data come from good subliminal encoders ($N = 24$; data collapsed over Encoding Intensity).

Table 4 | Comparisons between good and poor subliminal encoders.

Brain region	BA	Left/right	MNI-coordinates			*k*	*t*	*z*
			x	*y*	*z*			
GOOD > POOR SUBLIMINAL ENCODERS, ONE-TRIAL ENCODING (WORDS > NONWORDS)								
Middle cingulate gyrus	23	R	6	−14	30	39	4.41	3.72
Hippocampus		L	−30	−40	2	35	4.6	3.83
Hippocampus		L	−38	−20	−16	56	4.16	3.56
GOOD > POOR SUBLIMINAL ENCODERS, NINE-TRIAL ENCODING (LINEAR INCREASE)								
Postcentral gyrus	4	L	−60	−18	46	29	5.44	4.28
Hippocampus, rhinal cortex		L	−30	−16	−24	13	3.42	3.03
Rhinal cortex		R	26	−24	−20	23	3.64	3.19
INTERACTION OF RETRIEVAL CONDITION WITH SUBLIMINAL ENCODING QUALITY (ANALOGS > BROKEN ANALOGS, GOOD > POOR SUBLIMINAL ENCODERS)								
Parahippocampal gyrus		L	−20	−32	−16	51	3.9	3.74
Hippocampus		L	−40	−32	−4	19	3.26	3.17

N = 51; statistical maps thresholded at p = 0.005, k = 0 in medial and anterior temporal lobe regions, all other regions p = 0.001, k = 20.

words in supraliminal pairs that either retained a previously encoded semantic relation (analogs) or not (broken analogs). The successful unconscious detection of semantic relations in supraliminal test words that were analogous to semantic relations in subliminal encoding words was suggested by a larger number of fit responses given to analogs than broken analogs at test. Hence, episodically related versus unrelated words in test pairs were more often judged as closely related semantically. In other words, semantic relations encoded in an unconsciously experienced episode had intruded into judgments of semantic distance made at test. This effect corresponds to findings from supraliminal, i.e., conscious, stimulus processing. When two unrelated words, which had been presented in the same encoding context and were therefore episodically (but not semantically) related, were represented at test, they appeared closer semantically than words that had not been presented in the same encoding context; or they appeared equally close as words that were related semantically (McKoon and Ratcliff, 1979, 1986; Dosher and Rosedale, 1991; Patterson et al., 2009; Coane and Balota, 2011). This line of research suggests that connections between mental representations or between nodes in the semantic network, which have been co-activated in the same encoding context, acquire a greater linkage strength leading to the impression of stronger conceptual relatedness. The co-occurrence of concepts in naturalistic events is indeed one way how the

semantic system may be dynamically (re)organized throughout life (Coane and Balota, 2011). Although test pairs in the current study did not contain the subliminal encoding words but semantic neighbors thereof, the same principle seems to apply.

These modifications in the semantic system apparently relied on the relational binding of subliminal words in the hippocampus. The hippocampus is thought to assist the encoding of events by association formation between simultaneously activated areas of the neocortex (Teyler and DiScenna, 1986; Treves and Rolls, 1994). Because our task required a rapid relational encoding process with resulting flexible representations of word pairs (Cohen and Eichenbaum, 1993; Henke, 2010), we had hypothesized a role for the hippocampus in relational encoding and retrieval. Our neuroimaging results confirmed the expected involvement of the hippocampus and other structures of the episodic memory network during subliminal encoding and during unconscious retrieval in the test situation.

The current results emphasize the intimate relationship between memory and analogical reasoning. While previous neuroimaging studies of analogical reasoning made use of pre-existing knowledge stored in semantic memory that acted as source knowledge (Bunge et al., 2005; Green et al., 2006b, 2010), we aimed at the unconscious detection of analogies to episodic rather than semantic memories. Therefore, we had participants establish new episodic source knowledge in the experimental session. Due to our particular interest in unconscious analogical reasoning, we excluded conscious awareness already at the time of encoding the source episodes. Our finding of a successful unconscious detection of analogies between current and past episodes connects with purely behavioral studies of unconscious analogical reasoning, in which participants also encoded source information – although supraliminal source information – in the experimental session itself (Schunn and Dunbar, 1996; Day and Gentner, 2007; Day and Goldstone, 2011). The source knowledge gained in these studies was of a procedural (Day and Goldstone, 2011) or episodic nature (Schunn and Dunbar, 1996; Day and Gentner, 2007). Because all encoding material was presented suprathreshold for conscious inspection, information about conscious awareness of insight into analogies had to be determined with post-experimental questionnaires. This procedure is liberal because a potential conscious detection of analogies of a current with a past (conscious) learning situation may remain unreported. The subliminal presentation of the source information excludes consciousness of analogy detection more rigorously. That the presentation of encoding word pairs was indeed subliminal was demonstrated in our study by the participants' chance performance on the direct test of awareness (Greenwald et al., 1996; Snodgrass and Shevrin, 2006).

In line with studies of *conscious* analogical reasoning (Bunge et al., 2005; Green et al., 2006b, 2010; Speed, 2010; Knowlton et al., 2012), the largest signal change during *unconscious* analogy detection (analogs versus broken analogs) was located in the medial prefrontal cortex. Ventromedial (BA 10, 11) prefrontal areas are thought to promote the integration of distant semantic concepts as a means to achieve analogical mapping (Bunge et al., 2005; Green et al., 2006b, 2010). Perceived semantic distance is likely represented in medial prefrontal cortex because ventromedial prefrontal activity scaled positively with the semantic distance between two words in a pair, as reported in a study of conscious analogical reasoning (Green et al., 2010). In the present study, ventromedial prefrontal activity was reduced in response to analogs versus broken analogs, which corresponds to the subjective decrease in semantic distance of words in analogs versus broken analogs (see also Reber and Henke, 2011). At the intersection of memory and decision making, the ventromedial prefrontal cortex brings together the contents of long-term memory provided by the hippocampus and the planning abilities of prefrontal cortex to guide behavior (Euston et al., 2012; Guitart-Masip et al., 2013). We assume that the display of analogs in the test situation had triggered the reactivation of unconscious memories of subliminal word pairs through the medial temporal lobe, which in turn evoked a reinstatement of activity within the medial prefrontal cortex and other neocortical regions (McClelland et al., 1995). This reinstatement may have facilitated the processing of semantic relations between words in analogs.

The current findings show that the medial temporal lobe including hippocampus mediated unconscious relational encoding and the flexible retrieval of stored relations in the test situation, which enabled the unconscious detection of analogous relationships. Because the study format (e.g., table–car) differed from the test format (e.g., desk–bus), relational memories must have been expressed flexibly in the test situation. Hence, our data suggest that the encoding of new semantic relations and their flexible expression do not depend on conscious awareness of encoding and retrieval. This finding supports our notion that hippocampus-dependent relational encoding and retrieval may proceed with and without conscious awareness of encoding/retrieval (Henke, 2010) and questions views that link hippocampal processing and episodic memory to consciousness (Tulving, 1985; Reber and Squire, 1994; Squire and Zola, 1996; Squire et al., 2007; Moscovitch, 2008). The current and past findings of unconscious relational encoding (Henke et al., 2003a,b; Degonda et al., 2005; Duss et al., 2011; Reber and Henke, 2011, 2012; Reber et al., 2012) and past findings of unconscious relational retrieval (e.g., Greene et al., 2001; Leo and Greene, 2008; Hannula and Ranganath, 2009) are better accommodated by a memory model that divides between memory systems based on processing modes rather than consciousness (Henke, 2010).

Beyond memory, our results highlight the extent to which purely unconscious processes may contribute to higher-order cognition. Our study adds to a growing body of literature that pushes the boundaries of unconscious cognition into fields such as cognitive control (Van Gaal et al., 2008, 2010), decision making (Pessiglione et al., 2007, 2008), and free will (Soon et al., 2008). It becomes increasingly clear that our behavior and our conscious thoughts are deeply influenced by unconscious processes.

AUTHOR CONTRIBUTIONS

Thomas P. Reber designed and conducted the research, analyzed the data, and wrote the paper. Roger Luechinger and Peter Boesiger provided MR-Technology and infrastructure. Katharina Henke designed the research, analyzed the data, and wrote the paper.

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REFERENCES

Aggleton, J. P., Dumont, J. R., and Warburton, E. C. (2011). Unraveling the contributions of the diencephalon to recognition memory: a review. *Learn. Mem.* 18, 384–400. doi:10.1101/lm.1884611

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., et al. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat. Neurosci.* 6, 750–757. doi:10.1038/nn1075

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–2796. doi:10.1093/cercor/bhp055

Blumenfeld, R. S., and Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J. Neurosci.* 26, 916–925. doi:10.1523/JNEUROSCI.2353-05.2006

Bunge, S. A., Wendelken, C., Badre, D., and Wagner, A. D. (2005). Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. *Cereb. Cortex* 15, 239–249. doi:10.1093/cercor/bhh126

Cabeza, R., and Nyberg, L. (2000). Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* 12, 1–47. doi:10.1162/08989290051137585

Cavanna, A. E., and Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583. doi:10.1093/brain/awl004

Chee, M. W. L., O'Craven, K. M., Bergida, R., Rosen, B. R., and Savoy, R. L. (1999). Auditory and visual word processing studied with fMRI. *Hum. Brain Mapp.* 7, 15–28. doi:10.1002/(SICI)1097-0193(1999)7:1<15::AID-HBM2>3.0.CO;2-6

Coane, J. H., and Balota, D. A. (2011). Face (and nose) priming for book: the malleability of semantic memory. *Exp. Psychol.* 58, 62–70. doi:10.1027/1618-3169/a000068

Cohen, N. J., and Eichenbaum, H. (1993). *Memory, Amnesia, and the Hippocampal System*. Boston: MIT Press.

Day, S. B., and Gentner, D. (2007). Nonintentional analogical inference in text comprehension. *Mem. Cognit.* 35, 39–49. doi:10.3758/BF03195940

Day, S. B., and Goldstone, R. L. (2011). Analogical transfer from a simulated physical system. *J. Exp. Psychol. Learn. Mem. Cogn.* 37, 551–567. doi:10.1037/a0022333

Degonda, N., Mondadori, C. R. A., Bosshardt, S., Schmidt, C. F., Boesiger, P., Nitsch, R. M., et al. (2005). Implicit associative learning engages the hippocampus and interacts with explicit associative learning. *Neuron* 46, 505–520. doi:10.1016/j.neuron.2005.02.030

Dehaene, S., and Changeux, J.-P. (2011). Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227. doi:10.1016/j.neuron.2011.03.018

Dehaene, S., and Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition* 79, 1–37. doi:10.1016/S0010-0277(00)00123-2

Dosher, B. A., and Rosedale, G. (1991). Judgments of semantic and episodic relatedness-common time-course and failure of segregation. *J. Mem. Lang.* 30, 125–160. doi:10.1016/0749-596X(91)90001-Z

Duss, S. B., Oggier, S., Reber, T. P., and Henke, K. (2011). Formation of semantic associations between subliminally presented face-word pairs. *Conscious. Cogn.* 20, 928–935. doi:10.1016/j.concog.2011.03.018

Euston, D. R., Gruber, A. J., and McNaughton, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron* 76, 1057–1070. doi:10.1016/j.neuron.2012.12.002

Frank, M. J., Rudy, J. W., and O'Reilly, R. C. (2003). Transitivity, flexibility, conjunctive representations, and the hippocampus. II. A computational analysis. *Hippocampus* 13, 341–354. doi:10.1002/hipo.10084

Gentner, D. (1983). Structure-mapping: a theoretical framework for analogy. *Cogn. Sci.* 7, 155–170. doi:10.1207/s15516709cog0702_3

Gentner, D., Rattermann, M. J., and Forbus, K. D. (1993). The roles of similarity in transfer: separating retrievability from inferential soundness. *Cogn. Psychol.* 25, 524–575. doi:10.1006/cogp.1993.1013

Gilboa, A., Winocur, G., Grady, C. L., Hevenor, S. J., and Moscovitch, M. (2004). Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. *Cereb. Cortex* 14, 1214–1225. doi:10.1093/cercor/bhh082

Graves, W. W., Binder, J. R., Desai, R. H., Conant, L. L., and Seidenberg, M. S. (2010). Neural correlates of implicit and explicit combinatorial semantic processing. *Neuroimage* 53, 638–646. doi:10.1016/j.neuroimage.2010.06.055

Green, A. E., Fugelsang, J. A., and Dunbar, K. N. (2006a). Automatic activation of categorical and abstract nalogical relations in analogical reasoning. *Mem. Cognit.* 34, 1414–1421. doi:10.3758/BF03195906

Green, A. E., Fugelsang, J. A., Kraemer, D. J. M., Shamosh, N. A., and Dunbar, K. N. (2006b). Frontopolar cortex mediates abstract integration in analogy. *Brain Res.* 1096, 125–137. doi:10.1016/j.brainres.2006.04.024

Green, A. E., Kraemer, D. J. M., Fugelsang, J. A., Gray, J. R., and Dunbar, K. N. (2010). Connecting long distance: semantic distance in analogical reasoning modulates frontopolar cortex activity. *Cereb. Cortex* 20, 70–76. doi:10.1093/cercor/bhp081

Greene, A. J., Spellman, B. A., Levy, W. B., Dusek, J. A., and Eichenbaum, H. B. (2001). Relational learning with and without awareness: transitive inference using nonverbal stimuli in humans. *Mem. Cognit.* 29, 893–902. doi:10.3758/BF03196418

Greene, C. M., and Soto, D. (2012). Neural repetition effects in the medial temporal lobe complex are modulated by previous encoding experience. *PLoS ONE* 7:e40870. doi:10.1371/journal.pone.0040870

Greenwald, A. G., Draine, S. C., and Abrams, R. L. (1996). Three cognitive markers of unconscious semantic activation. *Science* 273, 1699–1702. doi:10.1126/science.273.5282.1699

Guitart-Masip, M., Barnes, G. R., Horner, A., Bauer, M., Dolan, R. J., and Duzel, E. (2013). Synchronization of medial temporal lobe and prefrontal rhythms in human decision making. *J. Neurosci.* 33, 442–451. doi:10.1523/JNEUROSCI.2573-12.2013

Hannula, D. E., and Ranganath, C. (2009). The eyes have it: hippocampal activity predicts expression of memory in eye movements. *Neuron* 63, 592–599. doi:10.1016/j.neuron.2009.08.025

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nat. Rev. Neurosci.* 11, 523–532. doi:10.1038/nrn2850

Henke, K., Treyer, V., Nagy, E. T., Kneifel, S., Dürsteler, M., Nitsch, R. M., et al. (2003a). Active hippocampus during nonconscious memories. *Conscious. Cogn.* 12, 31–48. doi:10.1016/S1053-8100(02)00006-5

Henke, K., Mondadori, C. R., Treyer, V., Nitsch, R. M., Buck, A., and Hock, C. (2003b). Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. *Neuropsychologia* 41, 863–876. doi:10.1016/S0028-3932(03)00035-6

Kiefer, M., and Martens, U. (2010). Attentional sensitization of unconscious cognition: task sets modulate subsequent masked semantic priming. *J. Exp. Psychol. Gen.* 139, 464–489. doi:10.1037/a0019561

Kirwan, C. B., Shrager, Y., and Squire, L. R. (2009). Medial temporal lobe activity can distinguish between old and new stimuli independently of overt behavioral choice. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14617–14621. doi:10.1073/pnas.0907624106

Knowlton, B. J., Morrison, R. G., Hummel, J. E., and Holyoak, K. J. (2012). A neurocomputational system for relational reasoning. *Trends Cogn. Sci.* 16, 373–381. doi:10.1016/j.tics.2012.06.002

Kreiman, G., Fried, I., and Koch, C. (2002). Single-neuron correlates of subjective vision in the human medial temporal lobe. *Proc. Natl. Acad. Sci. U.S.A.* 99, 8378–8383. doi:10.1073/pnas.072194099

Leech, R., Mareschal, D., and Cooper, R. P. (2008). Analogy as relational priming: a developmental and computational perspective on the origins of a complex cognitive skill. *Behav. Brain Sci.* 31, 357–377. doi:10.1017/S0140525X08004469

Leo, P. D., and Greene, A. J. (2008). Is awareness necessary for true inference? *Mem. Cognit.* 36, 1079–1086. doi:10.3758/MC.36.6.1079

Manelis, A., Paynter, C. A., Wheeler, M. E., and Reder, L. M. (2013). Repetition related changes in activation and functional connectivity in hippocampus predict subsequent memory. *Hippocampus* 23, 53–65. doi:10.1002/hipo.22053

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn. Sci.* 11, 126–135. doi:10.1016/j.tics.2006.12.003

McClelland, J. L., McNaughton, B. L., and O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights

from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457. doi:10.1037/0033-295X.102.3.419

McKoon, G., and Ratcliff, R. (1979). Priming in episodic and semantic memory. *J. Verbal Learning Verbal Behav.* 18, 463–480. doi:10.1016/S0022-5371(79)90255-X

McKoon, G., and Ratcliff, R. (1986). Automatic activation of episodic information in a semantic memory task. *J. Exp. Psychol. Learn. Mem. Cogn.* 12, 108–115. doi:10.1037/0278-7393.12.1.108

Morrison, R. G., Krawczyk, D. C., Holyoak, K. J., Hummel, J. E., Chow, T. W., Miller, B. L., et al. (2004). A neurocomputational model of analogical reasoning and its breakdown in frontotemporal lobar degeneration. *J. Cogn. Neurosci.* 16, 260–271. doi:10.1162/089892904322984553

Moscovitch, M. (2008). The hippocampus as a "stupid," domain-specific module: implications for theories of recent and remote memory, and of imagination. *Can. J. Exp. Psychol.* 62, 62–79. doi:10.1037/1196-1961.62.1.62

Müller, N. G., Strumpf, H., Scholz, M., Baier, B., and Melloni, L. (2013). Repetition suppression versus enhancement – it's quantity that matters. *Cereb. Cortex* 23, 315–322. doi:10.1093/cercor/bhs009

Murray, L. J., and Ranganath, C. (2007). The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *J. Neurosci.* 27, 5515–5522. doi:10.1523/JNEUROSCI.0406-07.2007

Patterson, K., Nestor, P. J., and Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat. Rev. Neurosci.* 8, 976–987. doi:10.1038/nrn2277

Patterson, M. M., Light, L. L., Van Ocker, J. C., and Olfman, D. (2009). Discriminating semantic from episodic relatedness in young and older adults. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 16, 535–562. doi:10.1080/13825580902866638

Pergola, G., Güntürkün, O., Koch, B., Schwarz, M., Daum, I., and Suchan, B. (2012). Recall deficits in stroke patients with thalamic lesions covary with damage to the parvocellular mediodorsal nucleus of the thalamus. *Neuropsychologia* 50, 2477–2491. doi:10.1016/j.neuropsychologia.2012.06.019

Pessiglione, M., Petrovic, P., Daunizeau, J., Palminteri, S., Dolan, R. J., and Frith, C. D. (2008). Subliminal instrumental conditioning demonstrated in the human brain. *Neuron* 59, 561–567. doi:10.1016/j.neuron.2008.07.005

Pessiglione, M., Schmidt, L., Draganski, B., Kalisch, R., Lau, H., Dolan, R. J., et al. (2007). How the brain translates money into force: a neuroimaging study of subliminal motivation. *Science* 316, 904–906. doi:10.1126/science.1140459

Quiroga, R. Q., Mukamel, R., Isham, E., Malach, R., and Fried, I. (2008). Human single-neuron responses at the threshold of conscious recognition. *Proc. Natl. Acad. Sci. U.S.A.* 105, 3599–3604. doi:10.1073/pnas.0707043105

Reber, P. J., and Squire, L. R. (1994). Parallel brain systems for learning with and without awareness. *Learn. Mem.* 1, 217–229.

Reber, T. P., and Henke, K. (2011). Rapid formation and flexible expression of memories of subliminal word pairs. *Front. Psychol.* 2:343. doi:10.3389/fpsyg.2011.00343

Reber, T. P., and Henke, K. (2012). Integrating unseen events over time. *Conscious. Cogn.* 21, 953–960. doi:10.1016/j.concog.2012.02.013

Reber, T. P., Luechinger, R., Boesiger, P., and Henke, K. (2012). Unconscious relational inference recruits the hippocampus. *J. Neurosci.* 32, 6138–6148. doi:10.1523/JNEUROSCI.5639-11.2012

Ridderinkhof, K. R. (2004). The role of the medial frontal cortex in cognitive control. *Science* 306, 443–447. doi:10.1126/science.1100301

Schmidt, C. F., Degonda, N., Luechinger, R., Henke, K., and Boesiger, P. (2005). Sensitivity-encoded (SENSE) echo planar fMRI at 3T in the medial temporal lobe. *Neuroimage* 25, 625–641. doi:10.1016/j.neuroimage.2004.12.002

Schunn, C., and Dunbar, K. (1996). Priming, analogy, and awareness in complex reasoning. *Mem. Cognit.* 24, 271–284. doi:10.3758/BF03213292

Segaert, K., Menenti, L., Weber, K., Petersson, K. M., and Hagoort, P. (2012). Shared syntax in language production and language comprehension – an FMRI study. *Cereb. Cortex* 22, 1662–1670. doi:10.1093/cercor/bhr249

Silberman, Y., Miikkulainen, R., and Bentin, S. (2005). Associating unseen events: semantically mediated formation of episodic associations. *Psychol. Sci.* 16, 161–166. doi:10.1111/j.0956-7976.2005.00797.x

Snodgrass, M., and Shevrin, H. (2006). Unconscious inhibition and facilitation at the objective detection threshold: replicable and qualitatively different unconscious perceptual effects. *Cognition* 101, 43–79. doi:10.1016/j.cognition.2005.06.006

Soon, C. S., Brass, M., Heinze, H.-J., and Haynes, J.-D. (2008). Unconscious determinants of free decisions in the human brain. *Nat. Neurosci.* 11, 543–545. doi:10.1038/nn.2112

Speed, A. (2010). Abstract relational categories, graded persistence, and prefrontal cortical representation. *Cogn. Neurosci.* 1, 126–137. doi:10.1080/17588921003660728

Spellman, B. A., Holyoak, K. J., and Morrison, R. G. (2001). Analogical priming via semantic relations. *Mem. Cognit.* 29, 383–393. doi:10.3758/BF03196389

Squire, L. R., Wixted, J. T., and Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nat. Rev. Neurosci.* 8, 872–883. doi:10.1038/nrn2154

Squire, L. R., and Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13515–13522. doi:10.1073/pnas.93.24.13515

Stoeckel, C., Gough, P. M., Watkins, K. E., and Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex* 45, 1091–1096. doi:10.1016/j.cortex.2008.12.004

Teyler, T. J., and DiScenna, P. (1986). The hippocampus memory indexing theory. *Behav. Neurosci.* 100, 147–154. doi:10.1037/0735-7044.100.2.147

Treves, A., and Rolls, E. T. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus* 4, 374–391. doi:10.1002/hipo.450040319

Tulving, E. (1985). How many memory-systems are there. *Am. Psychol.* 40, 385–398. doi:10.1037/0003-066X.40.4.385

Turk-Browne, N. B., Yi, D. J., and Chun, M. M. (2006). Linking implicit and explicit memory: common encoding factors and shared representations. *Neuron* 49, 917–927. doi:10.1016/j.neuron.2006.01.030

Van Gaal, S., Ridderinkhof, K. R., Fahrenfort, J. J., Scholte, H. S., and Lamme, V. A. F. (2008). Frontal cortex mediates unconsciously triggered inhibitory control. *J. Neurosci.* 28, 8053–8062. doi:10.1523/JNEUROSCI.1278-08.2008

Van Gaal, S., Ridderinkhof, K. R., Scholte, H. S., and Lamme, V. A. F. (2010). Unconscious activation of the prefrontal no-go network. *J. Neurosci.* 30, 4143–4150. doi:10.1523/JNEUROSCI.2992-09.2010

Vannini, P., Hedden, T., Sullivan, C., and Sperling, R. A. (2012). Differential functional response in the posteromedial cortices and hippocampus to stimulus repetition during successful memory encoding. *Hum. Brain Mapp.* 34, 1568–1578. doi:10.1002/hbm.22011

Voss, J. L., Hauner, K. K. Y., and Paller, K. A. (2009). Establishing a relationship between activity reduction in human perirhinal cortex and priming. *Hippocampus* 19, 773–778. doi:10.1002/hipo.20608

Wharton, C. M., Holyoak, K. J., and Lange, T. E. (1996). Remote analogical reminding. *Mem. Cognit.* 24, 629–643. doi:10.3758/BF03201088

Winocur, G., Oxbury, S., Roberts, R., Agnetti, V., and Davis, C. (1984). Amnesia in a patient with bilateral lesions to the thalamus. *Neuropsychologia* 22, 123–143. doi:10.1016/0028-3932(84)90056-3

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The episodicity of verbal reports of personally significant autobiographical memories: Vividness correlates with narrative text quality more than with detailedness or memory specificity

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How can we tell from a memory report whether a memory is episodic or not? Vividness is required by many definitions, whereas detailedness, memory specificity, and narrative text type are competing definitions of episodicity used in research. We explored their correlations with vividness in personally significant autobiographical memories to provide evidence to support their relative claim to define episodic memories. In addition, we explored differences between different memory types and text types as well as between memories with different valences. We asked a lifespan sample ($N = 168$) of 8-, 12-, 16-, 20-, 40-, and 65-year-olds of both genders ($N = 27, 29, 27, 27, 28, 30$) to provide brief oral life narratives. These were segmented into thematic memory units. Detailedness of person, place, and time did not correlate with each other or either vividness, memory specificity, or narrative text type. Narrative text type, in contrast, correlated both with vividness and memory specificity, suggesting narrative text type as a good criterion of episodicity. Emotionality turned out to be an even better predictor of vividness. Also, differences between narrative, chronicle, and argument text types and between specific versus more extended and atemporal memories were explored as well as differences between positive, negative, ambivalent, neutral, contamination, and redemption memory reports. It is concluded that temporal sequentiality is a central characteristic of episodic autobiographical memories. Furthermore, it is suggested that the textual quality of memory reports should be taken more seriously, and that evaluation and interpretation are inherent aspects of personally significant memories.

Keywords: autobiographical memory, episodic memory, narrative, vividness, memory specificity, redemption sequence, autobiographical reasoning, life story

INTRODUCTION

We first sketch the conceptual commonalities and divergences between these three concepts: episodic memory, autobiographical memory, and narrative. From this we derive the principal aim of the study, i.e., to explore the feasibility of some defining properties of the concept of episodic memories by way of testing their intercorrelation, using vividness as an undisputed characteristic of episodicity. Then two additional aims of the study are introduced, namely to explore narrative and other text types and of specific compared to other memory types, as well as to explore differences between memory reports of different evaluative qualities.

Tulving (1972) initially introduced the term episodic memory to separate the domain of traditional memory research on learning of meaningless verbal material, from the emerging field of semantic models of knowledge representation. Episodic memories thus referred to the pairing of contiguous stimuli learned in a one-time experience in the laboratory. Later when Tulving (1983, 1985) moved on to study neurologically impaired patients, he radically shifted the reference of the term episodic memory to include not just the knowledge of something one has learned, but also the remembering of the when and where of learning, and to events of one's life. Tulving stressed the temporal nature of remembering both in terms of a sense of personal past as well as of the temporal structure of what is being remembered, i.e., the unfolding of an event. At the same time he tied the remembering of past experiences to a specific phenomenal quality, autonoetic consciousness. He defined it as an immediate awareness that the remembered episode has been personally experienced. Other authors use the term "recollective experience" for remembering personal experiences (e.g., Conway, 2009). Because Tulving observed in a neurological patient K. C. that his total retrograde and anterograde amnesia was accompanied by an inability to imagine future actions and scenarios, he expanded the term autonoetic consciousness to include imagining the personal future. Thus the term defines the experience of having an extended existence in time, or a sense of personal continuity (for a narrative critique of this claim see Habermas and Köber, in press). Wheeler et al. (1997) further specified that the episodic memory system enabled

individuals to relive past experiences and imagine living through future events. They specified that episodic memory produced the subjective experience of an event, thereby tying episodic memory to the ability to differentiate one's own subjective perspective from those of others. Remembering from a subjective perspective entails a subjective visual perspective as well as memory of first person experiences such as perceptions, emotions, thoughts, and intentions. Thus at this point the term episodic memory came to include not only remembering, but also imagining hypothetical or future event sequences, deemphasizing the criterion of veridicality.

How can the episodic quality of a memory be judged objectively from a verbal memory report? In an influential paper, Levine et al. (2002) measured the episodic versus semantic quality of verbal reports of autobiographical memories by counting the number of clauses providing information about events, time, place, perceptions, and thoughts and emotions as well as global ratings of the maximum detailedness of the reports. A weakness of these measures is that they strongly depend on the length of the memory report, although the global ratings of detailedness, which were also used, do so to a far lesser degree.

A second tradition of memory research evolved in parallel to the concept of episodic memory. Neisser (1982) pleaded for expanding the scope of memory research to memories of personal experiences from one's life. The term autobiographical memory (Robinson, 1986) was used for personal memories that are related to the development of the self. This could be seen in the reminiscence bump (Rubin et al., 1986), i.e., an oversampling of memories from adolescence and young adulthood in adults over age 40, which was related to adolescent identity development (Fitzgerald, 1988). Neisser (1986) suggested that autobiographical memory has a hierarchical, nested structure. Barsalou (1988) found that besides specific events taking place at a specific date autobiographical memory reports may also contain recurrent ("summarized") events and extended events that cover several days or weeks, such as a trip, both termed "generalized events." In Conway's (1990) hierarchical model of the structure of autobiographical memory event specific knowledge is nested in generalized events, which are nested in extended time lines covering longer periods of life, which in turn are integrated by the life story schema (Bluck and Habermas, 2000; Conway et al., 2004). The autobiographical memory system is closely tied to mental representations of the self (Conway and Pleydell-Pearce, 2000).

Thus autobiographical memory covers both autobiographical knowledge as well as autobiographical memories of varying temporal extension. In this terminology, specific events or specific memories overlap with Tulving's later understanding of episodic memories, although the memory of a specific event such as a birthday party may either just be known or actually be remembered as a sequence of perceived events, i.e., an episodic memory. Parts of this tradition stress the temporal specificity and limited extension of an event more than a sense of reliving or of personal continuity (for exceptions see, e.g., Conway, 2009). The measure of episodic versus semantic quality of autobiographical memories suggested by Kopelman et al. (1989) is closer to this tradition, as the episodicity of a memory is rated on a four-point scale ranging from specific events with temporal and locational details to no response or an answer based on knowledge.

A third, linguistic tradition may also contribute to an understanding of remembering past experiences, since these are communicated in language. This tradition categorizes types of texts according to their function and form. Narrative is a text type which serves to communicate an event by imitating the sequence of events, typically in sentences beginning "and then . . ., and then . . ., and then." Labov and Waletzky (1967) suggest that narrative clauses are at least two sequential main clauses, the referential meaning of which would change if their order was reversed. For instance, the clauses "John was hungry. John had dinner at the local restaurant" change meaning if their order was reversed. Instead of John going to the restaurant to appease his hunger, the sentences would then imply that the restaurant served portions too small to satisfy John's hunger. Labov and Waletzky point out that narrative texts have a second main function besides imitating an event sequence, namely that of evaluating the events. Evaluations are always made from a specific perspective, either by one of the participants of the event or from without, e.g., by the narrator. All mental expressions referring to a subjective point of view including all comments and interpretations by the narrator or any other individual are termed evaluations. Accordingly, narrative texts comprise not only narrative clauses, but also other kinds of clauses. When the narrator evaluates a past event by expressing an emotion, explaining or contextualizing the event, this is done in non-narrative clauses. Other text types that may be used in the context of remembering are chronicles (Linde, 1993) that summarize temporally structured events without imitating the sequence of events, and arguments that explain or justify statements (Rosenthal, 1995). If a text contains at least two narrative clauses, the text is considered a narrative (Labov and Waletzky, 1967), even though it typically also contains clauses with chronicles, arguments, and descriptions.

Episodic memories are most adequately communicated in narrative form, because specific episodes are temporally structured events. Reliving an event implies following the sequence of events. Actually narrating an event renders it easier to relive an episode than merely imagining it, because the narrative format requires a temporal and causal ordering of events. Narrative clauses, use of the protagonist's subjective perceptual perspective, and means of dramatic narrating such as historic present and direct speech facilitate a reliving for both narrator and listener (Nelson et al., 2008; Habermas and Diel, 2010). The use of emotion words is not necessary for a vivid narrative, as emotions are most directly elicited by the event sequence itself.

Comparing the narrative format to episodic memories, narratives need not be limited to a short duration or precise location, nor need they be told from the narrator's past perspective, but may also be narrated from someone else's or an objective, outside perspective. Also, although specific memories tend to be narrated and narratives tend to concern specific memories, these need not be narrated, but may be summarized. On the other hand, also extended events can be narrated, although usually there is a highly specific event at the core of a narrative, a complicating event.

In this paper we argue that the narrative format appears to best describe the textual form of reports of the subjective experience of remembering and reliving an event. We suggest that narrative is the textual form of reports of all subjective experiences covered by

Tulving's term autonoetic experience, which characterizes episodic memory. Similar to Tulving's definition, we deemphasize the role of details, which are important to measure the degree of veridicality of a memory. Instead we focus on the episodic, i.e., story-like nature of episodic memories which differentiates them from mere knowledge. Therefore a narrative approach agrees with Tulving that some non-autobiographical memories and experiences are to be included in the definition of episodic memories, such as memories of fictional stories. In this sense, as in everyday language use (episodic) memories are such irrespective of whether they regard personal experiences (autobiographical) or fictional stories, whether they are true or not.

Possible arguments for conceptually grouping episodic autobiographical memories with episodic memories of fictional or reported stories and with the experiences of daydreaming and anticipating future scenarios may be that all of these phenomena are simultaneously affected by a specific neurological damage, or that they activate the same brain regions, or similarities in the quality of subjective experience (Tulving, 2002). However, we argue that the subjective experience of reliving corresponds to a specific format, which is needed to communicate this experience, i.e., narrative. Under ideal conditions that minimize the probability of distortions, a narrative communication reflects a subjective experience of remembering or imaginatively living through an event. The narrative format of a verbal report obtained under ideal conditions is the best way to objectively judge the episodicity of memories and experiences. If this was true, the narrative quality of memory reports should correlate with another symptom of reliving, namely the vividness of a report.

In our study we set out to provide this evidence, comparing the empirical relation between vividness and aspects of the three definitions of remembering of personal experiences. We study these in the most personally significant memories possible, i.e., the ones included in life narratives. Therefore in adults these autobiographical memories are also most likely to be contextualized in the narrator's life to elaborate their biographical significance. This process of "autobiographical reasoning" (Habermas and Bluck, 2000; Habermas, 2011) is more than mere remembering of past experiences, and has been discarded as "external detail" in research on episodic memory (Levine et al., 2002). It is the essential way of processing autobiographical memories by tying them to other parts of life and to the development of the self. Thus life narratives contain both autobiographical memories and their evaluative, interpretative elaboration.

Whereas in earlier analyses (Habermas and de Silveira, 2008) we were interested in the global coherence of life narratives, here we segmented life narratives into thematic units comparable to memories to render comparison to research on isolated episodic memories easier. We then coded each segment separately for text type and memory specificity, and we rated detailedness of indications of time, place, and persons as approximations of the three definitions of remembering events from the personal past. We also rated vividness as an aspect that can be related to all three approaches.

The main aim of this study was to test how some of the suggested aspects of episodic autobiographical memories are related to vividness as a relatively undisputed characteristic of episodic memories. We assume that suggested aspects of episodic memories need to be correlated to vividness and other aspects that define episodic memories if they are to be accepted as defining or typical aspects. Thus if suggested criteria of the episodicity of memories fail to correlate with vividness and with other criteria, we suggest discarding them as defining elements of the episodicity of memories. Our expectation was that out of the three characteristics of personal memories, narrative is the best predictor of vividness because it establishes a gradual unfolding of the past sequence of events. This expectation is supported by the observation that when asked to tell familiar fairy tales, the aforementioned amnesic patient K. C. was able to name a relatively normal number of themes present in the tales, but failed to establish the correct order of these themes, offering disorganized, discoherent accounts (Rosenbaum et al., 2009). This does not point to a lack of either (semantic) knowledge or of memories of specific events as represented by the themes, but specifically to a lack of the ability to provide narrative structure to events. Finally, we expected the evaluation of past events in terms of emotions, interpretation, and integration of the event into the life story to be less related to vividness.

A second aim of the study was to explore differences between narrative and other text types and between specific and other kinds of memories. Given the current focus on episodic autobiographical memories, there is little research on other than specific types of memories and other than narrative types of text. Memories of recurrent events, for example, are relatively frequent in autobiographical accounts. In contrast to specific memories which tend to focus on the exceptional (Bruner, 1990), memories of repeated events may serve to underline the typical and habitual. For instance, when talking about one's childhood, sentences beginning with "We used to . . ." provide a sense of what it was like back then. A recent comparison of memory types evidenced that memories of recurrent events served more social functions, whereas specific and extended memories serve more self and directive functions (Waters et al., 2013). We expected both specific memories and narrative texts to be the most vivid and most detailed categories, chronicles and generalized event memories next, and arguments and memories of extended periods and comments last.

A third aim of the study was to explore differences between memory reports of differing valence. Negative events tend to be narrated more fully (Habermas et al., 2009b). Also, avoidance of specific memories and preference of repeated or extended events is typical for depressed individuals who may wish not to confront the specifics of negative events (Williams et al., 2007), which again suggests that specific memories are more negative than generalized memories or memories of entire periods.

We were interested not only in comparing positive with negative memories, but also in memories of mixed valence and especially in memories in which there is a change of valence. McAdams (2006) termed episodes in which valence shifts from bad to good redemption sequences, and episodes in which good turns bad contamination sequences. Redemption sequences are related to resilience, contamination sequences to depression (Lilgendahl and McAdams, 2011). The inclusion of sequences of changing valence pays tribute to the temporally sequential nature of (memory) narratives, which canonically start with a (positive or neutral) normal

state of affairs, then present a problem or complication, followed by attempts to solve it and a positive or negative outcome. Thus memories, especially if they are remembered sequentially like in a narrative, supporting reliving, are not always homogenous in valence. Rather complications usually provoke negative evaluations and emotions, while the final result may be a happy or not so happy end (cf. Habermas and Berger, 2011). We were interested in exploring differences between events of homogeneous and of mixed valence. This interest results from taking seriously the temporally sequential nature of episodic autobiographical memories, which is part of Tulving's later definition of episodic memory, but often not considered empirically.

Our data set had originally been collected to answer developmental questions. The four younger age groups have been used to study the development of global coherence in life narratives (Habermas and de Silveira, 2008; Habermas et al., 2009a). Some of the ratings and codings presented here have been used in a developmental analysis of the lifespan development of episodic memory and autobiographical reasoning (Habermas et al., in press). In this paper we do not pursue developmental interests. Rather, the extant age range of the participants serves to ensure that results can be generalized across almost the entire life span. The only age-related limitation is that autobiographical reasoning, reflected in the code life story integration, increases across adolescence (Habermas and de Silveira, 2008), and that the amount of detail and length of memory reports increase slightly between ages 8 and 16 (Willoughby et al., 2012) also in this sample.

MATERIALS AND METHODS

PARTICIPANTS

A total of 168 females and males from a central German city was distributed across six age groups (8, 12, 16, 20, 40, 65 years) with mean ages of 8.57 years (SD = 0.28, 14 girls, 13 boys), 12.38 (0.36, 14, and 15), 16.61 (0.43, 14, and 13), 20.52 (0.53, 13, and 14), 40.79 (2.87, 14, and 14), and 64.53 (2.27, 15, and 15). The youngest age group was the higher achieving half of third graders from a grade school, the adolescent and young adult groups were students of a Gymnasium, leading up to an "Abitur" which allows entry into university. Participants for the two oldest age groups were recruited with flyers distributed widely in local shops, at sports facilities, doctors' offices, and among continuing education University students. The younger age groups were heading toward an "Abitur," whereas 24 of the middle-aged and 19 of the older adults had "Abitur" or "Fachabitur," and 4 and 9 respectively had finished school after 10 years, with 2 of the older adults with a lower or no school degree. In the middle-aged group 14 held a College degree, 17 in the oldest group. Thus the four younger age groups were well-educated, and the educational level of the two older age groups was also well above average. Informed consent was obtained from all participants and from the parents of participants younger than 18 years.

PROCEDURE AND MATERIALS

The three younger age groups were interviewed individually by one of five different trained female interviewers in their mid-twenties in their schools, the three older age groups in our lab. Participants wrote seven most important memories from their lives each on a card, dated them, and put them in sequence on the table. Then they narrated their life in 15 min, integrating the seven memories and explaining how they have become the person they are today (cf. Habermas and de Silveira, 2008, for verbatim instructions). Participants were not interrupted except for a reminder of the time left after 10 min, and otherwise only encouraged to continue non-verbally. The seven memories served to ensure that specific episodes were integrated into the life story.

Segmenting

Verbatim transcripts were created from audio-files. They were divided into thematic segments containing at least four clauses (Diel et al., 2007). The prototype of a segment is a narrative focusing on a specific, datable event. Ideally segments are explicitly introduced and ended. Two research assistants independently segmented 16 entire life narratives $\kappa = 0.82$. Then each coder segmented half of the remaining narratives. To check the quality of the ensuing segmenting, another randomly chosen 16 narratives were coded also by the respective other coder, yielding $K = 0.92$. A deviation of a segment border of up to one clause was tolerated.

Coding

Segments served as basic units for coding, each segment receiving a code or rating (Diel et al., 2009). Ratings were made on scales ranging from 0 to 3 following Levine et al. (2002). Each point was defined in a manual. In the Appendix we present three examples of segments with their codes and ratings to illustrative purposes. For each participant, mean ratings and relative frequencies of codes were used. To measure interrater reliability, we used single intraclass correlations for ratings and Cohen's Kappa for nominal codes.

Detailedness of person, place, and time. Three aspects of the detailedness of information regarding persons, place, and time were rated. Person detail received a 3 if an individual was depicted very graphically with at least three details, a 2 if an individual was described with at least one additional information, a 1 if an individual was named, and a 0 if no or only anonymous people were mentioned. Place detail received a 3 if the location was precisely determined, e.g., by naming a specific building, a 2 if a location was named without allowing the identification of a precise place (e.g., the name of a long street), a 1 if only a generic place or a town was named, and a 0 if no location was named. Temporal detail was rated with a 3 if a date was provided, a 2 if a at least a year was provided, a 1 if the temporal indications were relatively imprecise, and a 0 if no temporal information was included that would allow a listener to roughly know when the event had taken place. Two raters independently rated person detail in 16 entire life narratives (261 segments), $r_{ic} = 0.83$. Then one of the two rated the remaining narratives. To check again the quality of the ensuing coding, another eight of these remaining narratives (140 segments) were rated also by the other rater, yielding $r_{ic} = 0.80$. Intraclass correlation for place detail was $r_{ic} = 0.86$ (0.82) and for time detail $r_{ic} = 0.84$ (0.87).

Vividness and emotions. For vividness, a value of 3 was given if the overall impression was very vivid and the segment included a

dramatized narration of a specific event, a 2 if the segment was fairly vivid and contained intensifiers like "very" and global evaluations like "it was just great," a 1 if the segment was not vivid and at the most one emotion label, global evaluation, or intensifier, and a 0 if the segment appeared dry and monotonous. Interrater reliabilities were $r_{ic} = 0.82$ (0.81). For emotions, 3 was rated if several emotions were named and at least one emotion was described in detail, a 2 if several emotions were only named, but not further specified, or if one emotion was named and elaborated, a 1 if one emotion was named, and a 0 if no emotion was named. Interrater reliabilities were $r_{ic} = 0.85$ (0.84) based on 261 (140) segments.

Text type and memory type. We coded two typologies of memory reports: memory specificity was taken from memory psychology and text type taken from linguistics. Although specificity aims at the content, text type at the form of text, they still should be highly related, because if specific events are talked about at length, they tend to be narrated. Following Barsalou (1988), we coded segments either as containing a specific memory of an event lasting up to a day, as generalized event, i.e., repeated events or events extending between a day and a year, as a period lasting longer than a year [approximating Conway's (1990) "lifetime period"], or as a segment that does not refer to a temporal unit, such as a comment. Interrater reliabilities were $\kappa = 0.81$ (0.71) based on 261 (140) segments.

Additionally, segments were coded as a narrative text if it contained at least two consecutive narrative clauses referring to consecutive events (Labov and Waletzky, 1967), as a chronicle, if it was not coded as narrative and the main bulk of the segment summarized events (Linde, 1993), or as an argument, if it was not coded as a narrative and the main part of the segment contained evaluations or interpretations (Rosenthal, 1995). Interrater reliabilities were $\kappa = 0.83$ (0.79) based on 250 (140) segments.

Life story integration and interpretation. We rated the degree to which the segment was related to other parts of the life story and the degree to which it was interpreted. Life story integration was rated 3 if the segment contained at least three references to other times or to other topics in life, 2 for two, 1 for one, and 0 for none such reference. Interpretation was rated 3 if the significance of the segment for one's life, a change in personality, or a profound change of attitude was described, 2 if the narrator described her or his own personality, explained emotional reactions, or gave a meaning to the event, 1 if an event was evaluated positively or negatively or emotions were mentioned, and 0 if events were only factually narrated, but not evaluated. Life story integration achieved an interrater reliability of $r_{ic} = 0.81$ (0.31), interpretation of $r_{ic} = 0.82$ (0.60), based on 337 (140) segments.

Valence. We coded the overall valence of the segment with six categories: neutral, ambivalent, positive, negative, initially negative turns out well (redemption sequence), and initially good turns bad (contamination sequence; McAdams, 2006). Interrater reliabilities were $\kappa = 0.80$ (0.75) based on 250 (140) segments. We also constructed a continuous variable of valence (used in **Table 1**), assigning −2 to contamination, −1 to negative valence, 0 to neutral and ambivalent segments, 1 to positive segments, and 2 to redemption sequences.

Age of memory. The age of each segment was judged in terms of age at the beginning and age at the end of the period covered by the segment, which were then averaged. Interrater reliabilities were $r_{ic} = 0.94$ (0.95) for the averaged values used here, based on 15 life narratives with 249 segments (5 life narratives, 88 segments).

RESULTS

Descriptive statistics at the level of individuals use ANOVAs. Since we are interested in relations between different aspects of life narrative segments, we analyze at the level of segments. In addition, because a varying number of several segments belongs to the same life narrative by the same narrator ($n = 3075$, $N = 168$), segments are not independent measurements. Therefore we mostly provide measures of the magnitude of differences or correlations. To provide some information about probabilities, we will aggregate

Table 1 | Correlations between aspects of memory reports ($N = 3075$ segments, upper right triangle) and means of correlations within participants ($N = 168$ participants, lower left triangle; significant correlations in bold).

		1	2	3	4	5	6	7	8	9	10	11	12
1	Vividness		0.13	−0.04	0.00	0.03	0.28	0.49	0.38	0.18	−0.01	−0.15	0.46
2	Detail of person	0.11		0.07	0.02	−0.02	0.04	0.09	0.02	0.17	−0.04	−0.01	0.20
3	Detail of place	0.01	0.06		0.09	0.00	0.02	−0.06	−0.07	0.08	0.03	0.22	0.13
4	Detail of date	−0.04	0.03	0.08		−0.02	−0.07	0.00	0.01	0.19	0.06	0.01	0.07
5	Specific memory	−0.01	−0.02	−0.01	0.01		0.30	0.07	0.00	−0.05	−0.04	−0.06	0.06
6	Narrative text	**0.28**	0.08	0.02	−0.08	**0.29**		0.13	0.00	0.02	−0.06	−0.10	0.31
7	Emotion	**0.60**	0.07	−0.03	−0.02	0.02	0.02		0.25	0.13	−0.05	−0.09	0.31
8	Interpretation	**0.45**	0.03	−0.04	−0.02	0.04	0.07	**0.32**		0.18	0.02	−0.02	0.32
9	Life story integr.	**0.19**	**0.19**	0.04	0.18	−0.04	0.03	0.15	**0.16**		0.01	0.02	0.35
10	Valence	0.01	−0.04	0.08	0.03	−0.05	−0.05	−0.05	0.01	0.05		−0.06	−0.05
11	Age of memory	−0.13	0.08	0.05	0.05	**0.17**	−0.03	−0.13	−0.08	−0.02	−0.05		−0.02
12	Segment length	**0.52**	**0.23**	**0.23**	0.05	0.08	**0.37**	**0.37**	**0.35**	**0.38**	−0.03	−0.11	

Only for mean correlations within participants (lower left triangle): $p < 0.05$ if $r > 0.15$, $p < 0.01$ if $r > 0.19$, $p < 0.001$ if $r > 0.27$.

correlations for each individual to test hypothesis 1. We will comment on correlations not under 0.15 and effect sizes indicating a prediction of variance of not below 2%. The corresponding correlation of 0.15 marks the lower limit of half of all correlations considered in a large set of meta-analytic studies (Hemphill, 2003). This lower limit also acknowledges that variables with only two to four points tend to result in relatively low correlations. This approach is tuned to the object of interest, i.e., qualities of segments measured repeatedly in varying numbers for each individual. It is also in line with the more exploratory nature of the study as well as with the recent stress on magnitude of effects rather than their probability.

DATA DESCRIPTION

Life narratives consisted of a mean of 241 propositions ($SD = 103.20$) and 18.31 segments ($SD = 6.90$). Segments contained a mean of 13.37 propositions ($SD = 3.57$). In ANOVAs with age group and gender as factors, length of life narratives both in terms of overall number of propositions [$F(5, 156) = 9.94$, $p = 0.000$, $\eta^2 = 0.24$] and number of segments [$F(5, 156) = 10.13$, $p = 0.000$, $\eta^2 = 0.25$] significantly varied with age, as did, to a lesser degree, mean number of propositions per segment [$F(5, 156) = 2.71$, $p = 0.022$, $\eta^2 = 0.08$]. Increase in length of entire narratives and of segments was linear with age, with the exception of the 40-year-olds for life narrative length and an exception of the 65-year-olds for segment length. There were no overall gender differences.

CORRELATIONS BETWEEN POSSIBLE INDICATORS OF EPISODICITY

To explore the relation between possible indicators of episodicity, we calculated all correlations on the basis of all segments ($N = 3075$; **Table 1**, upper right triangle). To enable us to test the significance of correlations and of differences between them, we also calculated all correlations within individuals, then transformed them to Fisher's z-values, and then averaged them across individuals (**Table 1**, lower left triangle). Among the correlations between aspects of memory reports which have been proposed as aspects of the episodicity of memories, i.e., the first six aspects in **Table 1**, there was an expected correlation between narrative and memory specificity ($r = 0.29$) and between narrative and vividness ($r = 0.28$). All the other correlations between the first six variables are negligible. Thus the measures of detailedness of persons, place, and time correlated neither with each other nor with vividness, narrativity, or memory specificity. To compare correlations with vividness, we calculated t-tests for dependent correlations. Narrativity indeed correlated significantly more with vividness than memory specificity, $t(134) = 2.97$, $p < 0.01$ and also more than detailedness, $t(158) = 1.98$, $p < 0.05$.

Segment length correlated most with vividness, and also, to a lesser degree, with narrativity, emotionality, interpretation, and life story integration. Related aspects correlated with each other, such as vividness and emotionality, and interpretation and life story integration. Unexpectedly, interpretation correlated strongly with vividness, and, to a lesser degree, with emotionality. Separate correlations for the three pairs of adjoining age groups revealed the same pattern of correlations. Only correlations with life story integration were larger in older age groups, due to the near absence of life story integration in lower age groups (cf. Habermas and de Silveira, 2008; Habermas et al., in press).

For descriptive purposes, we also ran a principal components analysis with correlations between all segments. Two components resulted from a screen test, explaining 22.2 and 13.1% of variance respectively. After varimax rotation the first component had loadings of 0.79 for vividness, 0.77 length, 0.64 emotion, 0.55 interpretation, 0.46 life story integration, and 0.40 narrative text format. Component 2 had loadings of 0.53 for life story integration, 0.50 for detail of place, 0.48 for temporal detail, −0.44 for narrativity and −0.41 for specificity, and 0.40 for age of memory. All other loadings were below 0.3. The first component may be interpreted to assemble characteristics of the episodicity of the verbal report, with a surprising, though low loading of life story integration. The second component may be interpreted to represent aspects of verbal reports that help locate events in life, in time, in space, which plausibly appears to be more necessary for older memories.

CONCURRENT PREDICTION OF VIVIDNESS AS PROXY FOR EPISODICITY

Taking vividness as the most uncontroversial proxy for episodicity of a memory report among the variables coded here, we explored the simultaneous correlations of possible indicators of episodicity on vividness. To this end we ran three stepwise regressions on vividness, entering all variables that explain more than 1% of variance to explore the variables' relative contributions in predicting vividness ($N = 3075$ segments). First we used only the five possible indicators of episodicity. Narrative text format predicted 7.9% of variance ($\beta = 0.28$), person detail added another 1.4% (corrected $R^2 = 0.091$, $\Delta R^2 = 0.014$, $\beta = 0.12$). However, when segment length was added, it predicted 21.5% of variance ($\beta = 0.46$), reducing the contribution of narrative text to 2% (corrected $R^2 = 0.235$, $\Delta R^2 = 0.020$, $\beta = 0.15$). Entering all variables in a third regression analysis left this contribution of narrative text intact: emotionality (corrected $R^2 = 0.242$, $\beta = 0.49$), segment length (corrected $R^2 = 0.350$, $\Delta R^2 = 0.108$, $\beta = 0.35$), interpretation (corrected $R^2 = 0.383$, $\Delta R^2 = 0.034$, $\beta = 0.20$), and narrative text (corrected $R^2 = 0.406$, $\Delta R^2 = 0.023$, $\beta = 0.16$). Out of the five suggested indicators of episodicity, narrative text format is still the best predictor of vividness even when used concurrently with segment length and all other variables to predict vividness. However, the effect size of narrative text format is reduced substantially by adding segment length from 8% to only 2%.

The unexpected correlation between vividness and interpretation might have to do with the way we operationalized interpretation: a 1 had been assigned if an emotion was not just transported by the plot, but was actually put in words and named. This is a very basic way of interpreting lived experience and does not carry with it the cognitive and distancing flavor stronger interpretation does. Also this definition of a rating of 1 for interpretation is similar to how a 1 for emotion was assigned. This explanation of the correlation between vividness and interpretation was confirmed when comparing mean vividness ratings for segments with interpretation values of 0, 1, and 2 or 3: while an interpretation rating of 0 was low in vividness ($M = 0.77$, SD = 0.63), there was no difference in vividness between an interpretation rating of 1 ($M = 1.68$, SD = 0.73) and 2 or 3 ($M = 1.66$, SD = 0.78). Accordingly separate correlations between vividness and a dichotomous variable

with a 1 for a 1 in interpretation and a 0 for all other interpretation ratings was higher ($r = 0.28$) than between vividness and a dichotomous variable with a 0 for interpretation ratings below 2 and a 1 for interpretation ratings of 2 or 3 ($r = 0.18$). The reverse pattern showed for correlations of the two dichotomous interpretation variables with life story integration ($r = 0.16$). Thus the correlation between vividness and interpretation is driven by the naming of emotions, but not by stronger forms of interpretation.

DIFFERENCES BETWEEN TEXT TYPES AND MEMORY TYPES

We explored differences between text types and memory types, focusing on narratives and specific memories as the types that come closest to specific episodic autobiographical memories. Out of a total of 3075 segments, 34.8% were narratives, 33.1% chronicles, and the remaining 32.1% arguments. Regarding memory types, 17.4% were specific memories, 49.7% extended events lasting more than a day and up to a year, 19.7% periods lasting over a year, and 13.2% atemporal comments (**Table 2**). Of the specific memories 66.3% were narrations, and 33.1% of narratives regarded a specific memory. Thus most specific memories tend to be narrated, but narratives may also cover longer time stretches.

Text type explained more variance of ratings and length than did memory type (**Table 3**). Most notably, text type explained 8% of variance in length of segment and 6% of variance in vividness. Narrative was the longest and most vivid text type. Memory type, in contrast, only explained 4% of variance of detailedness of persons. Comments were most detailed regarding persons, apparently regarding comments on enduring aspects of individuals. Although on average specific memories were the longest and the most vivid segments, these differences did not account for more than 0.5 and 0.3% of variance respectively. It is interesting to note that both in terms of text type and memory type, detailedness tended to be greatest in segments summarizing events and covering long stretches of time or repeated events. Thus detailedness in terms of person, place, and time was not a characteristic of narrative nor specific memories.

VALENCE: POSITIVE AND NEGATIVE SEGMENTS, REDEMPTION, AND CONTAMINATION SEQUENCES

Finally we explored whether events of differing valence also differed in other respects. All segments were coded for valence, with 40.4% positive segments, 23.0% negative, 13.2% ambivalent, and 8.8% neutral, and with 10.0% redemption sequences in which an initially negative state turned out well, and 4.6% contamination sequences in which an initially positive state turned out negative.

Segment valence explains the most variance in ratings and length (**Table 3**) regarding vividness (7%), emotion (5%), and length of segment (4%), and to a lesser degree, also some variance of interpretation and life story integration (2%). The general trend with all these aspects is that redemption, then contamination and ambivalent segments are longest, most vivid and emotional, and also most interpreted and linked to other parts of life, followed by negative, then positive, and finally neutral segments. Thus segments in which there is a sequence of actions with a change of fortune are, not surprisingly, the most vivid and emotional texts, followed by texts with more stationary mixed emotions.

Table 2 | Crosstabulation of text type with memory types.

Text type	Memory type – event				
	Specific	**Generalized**	**Long**	**Comment**	**Total**
Narrative	354	494	124	97	1069
	16.8	*−2.8*	*−8.3*	*−4.9*	
Chronicle	94	565	268	91	1018
	−8.2	*4.5*	*6.5*	*−4.9*	
Argument	86	470	215	217	988
	−8.7	*−1.6*	*1.9*	*9.9*	
Total	534	1529	607	405	3075

Rows in italics indicate corrected residuals per cell.

With regard to the contingencies of valence with text type and memory type (**Table 4**), negative segments were most frequently narrated as expected, redemption sequences were more often narratives or chronicles, and contamination sequences were most often chronicles, followed by narratives. A similar, but less pronounced pattern showed in memory types. Negative segments were most frequently found in specific memories, redemption sequences in specific and extended memories, and contamination sequences in extended events.

DISCUSSION

SUMMARY

Evaluation and narrative text format characterize episodic autobiographical memories

Comparing various characteristics of episodic autobiographical memories, vividness, emotion naming, and narrative text type correlated most with each other. Neither memory type nor detailedness of person, place, or time covaried with vividness as the most uncontroversial indicator of the episodicity of a memory, nor did indicators of detailedness correlate with each other. Detailedness is thus not a correlate of remembering an episode, i.e., a sequence of related actions and events. Static memories of what one's childhood home looked like or of one's parents' characters may be quite detailed without referring to events. Actually detailedness of persons was highest in comments, which apparently contained reflections on a person or relationship. Detailedness of place and time were highest in memory reports covering long life periods and in chronicles, suggesting that not so much memories of very specific events but rather summary reports of long stretches of life, like one's time in elementary school, require detailed local and temporal background information.

Apparently specific memories (limited to 1 day) are not especially vivid either. Rather it seems to be the sequential way in which events are presented in the text by narrating, and not just summarizing them, which contributes most to the vividness of the memory report. This finding supports the notion that episodic memories at the level of experiencing involve the reliving of an event, which implies most importantly imagining the events in a temporal forward fashion. Temporal sequentiality is one of the two constitutive aspects of narrative. While Tulving's concept of episodic memories focuses on the subjective experiential level, and narrative focuses on objective textual aspects of memories,

Table 3 | Text types, memory types, and valence (means, standard deviations in italics, effect sizes).

	Vividness	Detailedness			Life story integration	Interpretation	Emotion	Text length
		Person	Place	Time				
Total	1.44	1.21	0.91	1.11	0.65	1.11	0.56	13.20
	0.82	*0.78*	*0.72*	*0.91*	*0.73*	*0.91*	*0.86*	*8.59*
TEXT TYPE								
Narrative	1.75	1.25	0.95	1.02	0.62	1.11	0.71	16.9
	0.87	*0.71*	*0.67*	*0.91*	*0.74*	*0.87*	*0.95*	*10.5*
Chronicle	1.27	1.19	1.06	1.29	0.77	1.07	0.49	12.0
	0.75	*0.79*	*0.71*	*0.87*	*0.77*	*0.93*	*0.81*	*6.8*
Argument	1.26	1.19	0.75	1.02	0.54	1.14	0.47	10.5
	0.73	*0.84*	*0.71*	*0.93*	*0.65*	*0.92*	*0.80*	*6.3*
η^2	0.06	0.01	0.02	0.01	0.01	0.00	0.01	0.08
MEMORY TYPE								
Specific	1.49	1.17	0.92	1.07	0.57	1.09	0.69	14.4
	0.85	*0.65*	*0.70*	*1.00*	*0.68*	*0.84*	*0.92*	*9.4*
Generalized	1.46	1.14	0.91	1.10	0.61	1.10	0.54	12.9
	0.80	*0.76*	*0.68*	*0.90*	*0.72*	*0.92*	*0.85*	*8.4*
Long period	1.38	1.20	1.10	1.31	0.80	1.14	0.49	13.4
	0.85	*0.80*	*0.70*	*0.80*	*0.77*	*0.94*	*0.82*	*8.6*
Comment	1.38	1.57	0.72	0.90	0.67	1.08	0.56	12.5
	0.81	*0.88*	*0.74*	*0.96*	*0.74*	*0.92*	*0.86*	*8.3*
η^2	0.00	0.04	0.02	0.01	0.01	0.00	0.00	0.01
IMPLICIT VALENCE								
Neutral	0.81	1.15	1.00	1.23	0.50	0.69	0.14	9.7
	0.74	*0.81*	*0.78*	*0.97*	*0.65*	*0.91*	*0.47*	*5.5*
Positive	1.41	1.18	0.94	1.14	0.60	1.11	0.44	12.0
	0.78	*0.78*	*0.71*	*0.92*	*0.71*	*0.91*	*0.74*	*7.2*
Negative	1.52	1.24	0.90	0.98	0.61	1.12	0.69	13.8
	0.83	*0.76*	*0.69*	*0.89*	*0.72*	*0.87*	*0.94*	*9.1*
Ambivalence	1.56	1.32	0.88	1.17	0.75	1.23	0.68	15.6
	0.80	*0.78*	*0.69*	*0.90*	*0.77*	*0.92*	*−0.93*	*9.9*
Redemption	1.65	1.17	0.94	1.13	0.85	1.25	0.82	15.5
	0.83	*0.74*	*0.70*	*0.90*	*0.75*	*0.95*	*1.01*	*10.0*
Contamination	1.59	1.25	0.84	1.03	0.80	1.09	0.74	15.4
	0.75	*0.82*	*0.66*	*0.83*	*0.79*	*0.77*	*0.99*	*10.2*
η^2	0.07	0.00	0.00	0.01	0.02	0.02	0.05	0.04

both share temporal sequentiality as the core element. However, in memory research this temporally sequential aspect of memories is rarely studied, but mostly inferred once participants state that they remember an event, or it is judged from verbal memory reports, i.e., narratives.

The explicit and communicative nature of a narrative supports following a temporal sequence, whereas tacit remembering requires less temporal order. More probably tacit remembering involves thinking of specific situations, images, or impressions, which in remembering need not be brought into a sequential order. Thus it could well be that it is the narrative text format that more strongly induces a sequential reliving than mere remembering does. This would imply that the sequential aspect of reliving depends less on the memory system, save in some cases like traumatic memories (Rubin et al., 2008), but on the manifest linguistic shaping of the memory.

Aspects of the second constituent of narrative, the evaluation of the events, contributed even more to vividness. There are varying degrees of distancing involved in evaluation. Internal evaluations (Labov and Waletzky, 1967) arise from within the storyline and are made from the points of view of the past protagonists, while external evaluations are by others and from more distanced temporal perspectives. In our study, the naming of emotions substantially correlated with vividness, as did, to a lesser degree, interpretation. For the latter, the more distanced forms of interpreting did not add to vividness over and above the mere naming of emotions. The most distanced form of interpretation, integrating the remembered event into the life story, still correlated positively, if more moderately with vividness.

Finally the mere length of a memory report correlated not only with vividness, but also with emotion, narrativity, interpretation, and life story integration. Thus the length of a memory

Table 4 | Crosstabulation of evaluative patterns with text and memory types.

Evaluative pattern	Memory type – event			
	Specific	**Generalized**	**Long**	**Comment**
Neutral	38	98	75	60
	−1.5	*−4.7*	*3.4*	*4.6*
Positive	188	606	258	190
	−2.7	*−0.9*	*1.2*	*2.9*
Negative	181	367	103	57
	6.6	*1.3*	*−4.0*	*−4.6*
Ambivalent	45	209	88	64
	−3.6	*0.8*	*1.1*	*1.7*
Redemption	65	167	54	20
	1.9	*1.8*	*−1.0*	*−3.6*
Contamination	17	82	29	14
	−1.7	*2.0*	*0.2*	*−1.2*
Sum	534	1529	607	405
	Text type			
	Narrative	**Chronicle**	**Argument**	**Sum**
Neutral	61	70	140	271
	−4.4	*−2.7*	*7.2*	
Positive	367	418	457	1242
	−5.0	*0.5*	*4.6*	
Negative	318	181	209	708
	6.5	*−4.9*	*−1.7*	
Ambivalent	135	144	127	406
	−0.7	*1.1*	*−0.4*	
Redemption	134	135	37	306
	3.5	*4.3*	*−7.9*	
Contamination	54	70	18	142
	0.8	*4.2*	*−5.1*	
Sum	1069	1018	988	3075

Rows in italics indicate corrected residuals per cell.

report seems to be driven by several of these aspects. Taking into account segment length substantially reduced the predictive value of narrative text, without altering its position relative to the other suggested attributes of episodicity. However, length in and of itself is not a variable of primary interest here, but depends on how much an event is narrated and how much it is evaluated. Therefore the prediction of vividness without using segment length reflects the relative influences of text qualities of interest more adequately.

To sum up, as expected narrativity was a stronger predictor of vividness than memory specificity and detailedness. In addition, basic levels of evaluation, i.e., naming emotions, contributed even more to vividness. The comparably small size of the effect of narrative text might be related to the dichotomous coding of narrativity. A rating of the degree of narrativity of memory reports would capture this aspect better and could very well increase its predictive power.

Exploration of types of memory reports

The typologies of memory reports revealed some interesting differences, more between text types and less between memory types. First, as expected narratives were more vivid than chronicles and arguments, whereas differences between memory types were minimal. Similarly, narratives were longer than chronicles and arguments, whereas the same trend was weaker for specific memories.

Text types also differed more than memory types with regard to evaluative patterns. As expected, negative events were disproportionately more frequent in specific and narrative memory reports. Redemption sequences were distributed equally across narratives and chronicles as well as specific and generalized events, whereas contaminations sequences were most frequent among chronicles and generalized events. This confirms that negative events tend to motivate more specific and more narrative memory reports than positive or neutral events. In terms of memory and text type, negative memories stuck out. However, memory reports with mixed evaluations, and especially those with a change of fortune stood out in terms of being the most vivid and emotional, the longest, but also the ones that were most often interpreted and integrated into the life story. Again this points to the importance of a narrative structure of memory reports, since narratives normatively contain changes of fortune as events unfold and actions fail or succeed.

LIMITATIONS

The autobiographical memories analyzed in this study were selected as highly self-defining, covered participants' entire lives, and were narrated by participants from a very wide age range. Therefore they may not be quite comparable to most of the more recent, less self-relevant memories from mostly young adults used in most research on episodic memory. However for example the tendency to produce specific or non-specific memories seems to be comparable when cued with words or asked to narrate self-defining memories (Sumner et al., 2013). In addition, the more personal nature and more diverse age ranges of both memories and participants should render results more relevant for various ages and personally salient autobiographical memories.

The study was correlational. This appears to be adequate if the object of interest is relationships and not causal effects. Memories were not explicitly elicited as memories, but were chunks of continuous life narratives. Thus some parts of life narratives may be produced less with the intention of providing memories but to follow the life line and fill in gaps between memories. Although this probably leads to the production of more non-specific memories than instructions to remember specific episodes, we would argue that regarding autobiographical memory this method provides a broader range of elements of autobiographical remembering more representative of the whole range of ways of autobiographical remembering. In more narrow and controlled studies, specific kinds of episodic memories might be elicited to explore whether defining characteristics are more characteristic under some recall conditions than others. For instance, going beyond the scope of this paper which was limited to autobiographical episodic memories, future studies might compare autobiographical with other kinds of episodic memories such as memories of routine activities,

dreams, daydreams, stories known from hearsay, and fictional stories as well as fantasized future scenarios in order to explore whether the autobiographical quality of memories sets them apart from other episodic memories in terms of the defining qualities of interest here.

Only four suggested criteria for the episodicity of memory reports were tested here. Future explorations of the episodicity of memories should also include other aspects of memory reports such as the perspective of mental references, the actual number of narrative clauses, or the completeness of the narrative structure, as well as subjective reports of a sense of remembering vs. knowing, of experiencing that the episode had been personally lived through before, and the intensity of a sense of reliving.

A more serious limitation was the partial semantic overlap between some constructs. This had not been intended when writing the manuals, but sometimes a more operational definition relying on specific indicators proved necessary to achieve the necessary interrater reliability. Specifically there was some overlap between emotion naming and the ratings of vividness and of interpretation. For the mid-range ratings of vividness emotion labels could be one indicator out of several possible. For a rating of 1 in interpretation the presence of emotion labels was sufficient. Although theoretically these definitions do make sense, ideally these two ratings would be defined without operational overlap. Finally participants were well-educated. This may have increased attempts to interpret memories and to integrate them into the life story.

IMPLICATIONS

Not detail, but temporal sequence makes autobiographical memories episodic

The degree of detail in terms of specifications of individuals, place, and time are not essential elements of episodic autobiographical memories. The importance of detail in the memory literature probably stems from memory research's focus on the veridicality of memory, and the field of episodic memory appears to be slowly shifting away from detailedness (Piolino et al., 2009). For many practical purposes, remembering detail is important, such as when witnessing a crime. Also when remembering important episodes of one's life veridicality is still a prime issue, since interlocutors do not want to be confronted with an invented life. However it is less the details of an event, but rather the event sequence itself, its causal-motivational internal structure and its meaning that matter. The precise geographical and temporal location is less important than what happened, who did what, why, and with what consequences, and what it tells about the narrator.

Both the temporal sequentiality and a structuring through intentional acts are implied by the choice of the term episode, which denotes a relatively self-contained part of a larger story. Temporal sequentiality is also implied by Tulving's definition of episodic memories as a reliving of experiences. Also the specificity of memories implies a temporal sequentiality, since it requires events with a temporal extension. But the limitation of the duration of specific memories to 1 day is somewhat arbitrary and reflects a too strong focus on detailedness. The centrality of temporal sequentiality for episodic autobiographical memories suggests that identifying the episodicity of memories objectively in memory reports should rely more on the event character of episodic memories than on atemporal details and dating.

Also, when studying the affective valence of memories, measuring only positive versus negative tone and affective intensity may miss important differences. Memories with conflicting evaluations and or even with a change of fortune, and especially memories of negative events with a happy ending, stand out as especially long, vivid, and emotional as well as involving more interpretation and integration into the life story. Memory reports differ both by the specific emotions involved as well as by the sequence of emotions (Habermas et al., 2009b) and sequence of positive versus negative evaluations (McAdams, 2006).

This insight has consequences for the study of memory in psychopathological states. Thus in depression memories tend not only to be less specific (Williams et al., 2007), but they also differ in their temporal structure. This not only means that in depression memories have less of an internal temporal extension, but also that a change from a positive to a negative evaluation in episodic memories is more frequent (Adler et al., 2006). In addition, depressed patents are more immersed in their past, as shows in a less linear temporal structure of life narratives and less stepping outside past episodes to comment on them (Habermas et al., 2008).

The textual quality of episodic memories is narrative

In a way important autobiographical memories require being narrated to oneself as well as to others. If a memory is really relived or, for that case, intensively experienced like a daydream, the events are visually and linguistically narrated to oneself. The normative form of narrative (Labov and Waletzky, 1967) requires not only a temporal ordering of events, but also their causal-motivational structuring so as to understand what happened. Thus a fully episodic autobiographical memory is more than the memory of a specific scene, but requires an interpreted sequence of events and actions.

This is in accordance with an understanding of the ability to remember as being culturally socialized (Nelson and Fivush, 2004; Habermas et al., 2010; Fivush et al., 2011) and of memories as being culturally framed, put into and formed by text, and communicated in language (Markowitsch and Staniloiu, 2011). Thus more attention should be paid to the actual textual and narrative qualities of autobiographical memories. Here we used a rating and global coding methodology which is more typical for memory research than for linguistic analyses. We have demonstrated narrative analyses of the textual surface of autobiographical memories of a more differentiated linguistic kind elsewhere (e.g., Habermas et al., 2009b), which might well increase the correlation of narrativity measures with vividness.

Autobiographical episodic memories are not only relived and narrated, they are also evaluated

There are varying degrees of the immediacy of evaluating, ranging from more affective to more cognitive modes, from perceptions to emotions and thoughts in the past to those from a present or hypothetical perspective, from immediate reactions to more effortful and complex interpretative efforts. This dimension implies varying degrees of narrative distancing from the past event. Past perceptions and past direct speech are very close to past experiences

(Habermas et al., 2008). Also the naming of emotions is relatively close to past events and therefore correlates highly with vividness.

Complex form of evaluation such as interpretation and autobiographical reasoning are more distanced forms of evaluation. Autobiographical reasoning establishes logical links between a past event and other, distant parts of life or with the narrator's personality and its development (Habermas and Bluck, 2000; Habermas, 2011). What we termed life story integration here, the mere mentioning of other parts of life or of personality, is a simple measure of autobiographical reasoning. Autobiographical reasoning goes beyond mere remembering by establishing the meaning of the past event for who the remembering person was and is. The ability for creating coherent life narratives and for autobiographical reasoning, i.e., a specifically biographical view on events, develops between late childhood and early adulthood, as was demonstrated in two studies (Bohn and Berntsen, 2008; Habermas and de Silveira, 2008). First studies of the location of brain activities correlated with autobiographical reasoning have also been undertaken (D'Argembeau et al., 2008, in press). In this study, interpretation and autobiographical reasoning were related to changes of fortune in the memory and to its vividness and emotionality.

Episodic memories of biographically non-salient events do not evoke much of an interpretation or autobiographical reasoning, which therefore can be ignored without a great loss. However the more potentially personally significant a past event is, the more autobiographical reasoning becomes part of the process of remembering, and the more it should be included in studies of episodic autobiographical memories.

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REFERENCES

Adler, J. M., Kissel, E. C., and McAdams, D. P. (2006). Emerging from the CAVE: attributional style and the narrative study of identity in midlife adults. *Cognit. Ther. Res.* 30, 39–51. doi:10.1007/s10608-006-9005-1

Barsalou, L. W. (1988). "The content and organization of autobiographical memories," in *Remembering Reconsidered: Ecological and Traditional Approaches to the Study of Memory*, eds U. Neisser and E. Winograd (New York: Cambridge University Press), 193–243.

Bluck, S., and Habermas, T. (2000). The life story schema. *Motiv. Emot.* 24, 121–147. doi:10.1023/A:1005615331901

Bohn, A., and Berntsen, D. (2008). Life story development in childhood. *Dev. Psychol.* 44, 1135–1142. doi:10.1037/0012-1649.44.4.1135

Bruner, J. (1990). *Acts of Meaning*. Cambridge, MA: Harvard University Press.

Conway, M. A. (1990). *Autobiographical Memory*. Buckingham: Open University Press.

Conway, M. A. (2009). Episodic memories. *Neuropsychologia* 47, 2305–2313. doi:10.1016/j.neuropsychologia.2009.02.003

Conway, M. A., and Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 107, 261–288. doi:10.1037/0033-295X.107.2.261

Conway, M. A., Singer, J. A., and Tagini, A. (2004). The self and autobiographical memory: correspondence and coherence. *Soc. Cogn.* 22, 491–529. doi:10.1521/soco.22.5.491.50768

D'Argembeau, A., Cassol, H., Philipps, C., Balteau, E., Salmon, E., and van der Linden, M. (in press). Brains creating stories of selves: the neural basis of autobiographical reasoning. *Soc. Cogn. Affect. Neurosci.* doi:10.1093/scan/nst028

D'Argembeau, A., Fevers, D., Maierus, S., Collette, F., van der Linden, M., Maquet, P., et al. (2008). Self-reflection across time: cortical midline structures differentiate between present and past. *Soc. Cogn. Affect. Neurosci.* 3, 244–252. doi:10.1093/scan/nsn020

Diel, V., Elian, C., and Weber, A. (2007). *Manual zur Thematischen Segmentierung Autobiographischer Erzählungen [Manual for Segmenting Autobiographical Narratives]*. Unpublished manual, Goethe University, Frankfurt.

Diel, V., Heberer, J., Kraaz, A., Mahmoudi, A., Streck, L., Habermas, T., et al. (2009). *Manual zum Kodieren von Lebendigkeit, Emotionsbenennungen, Interpretation, Integration in Die Lebensgeschichte, Detailliertheit, Valenz, Gedächtnistypen und Textsorten in Segmenten Autobiographischer Erzählungen [Manual for Coding Vividness, Emotion Naming, Interpretation, Life Story Integration, Detailedness, Valence, Memory Type, and Text Type in Segmented Autobiographical Narratives]*. Unpublished manual, Goethe University, Frankfurt.

Fitzgerald, J. M. (1988). Vivid memories and the reminiscence phenomenon: the role of a self narrative. *Hum. Dev.* 31, 261–273. doi:10.1159/000275814

Fivush, R., Habermas, T., Waters, T., and Zaman, W. (2011). The development of autobiographical memory. *Int. J. Psychol.* 46, 321–345. doi:10.1080/00207594.2011.596541

Habermas, T. (2011). "Autobiographical reasoning: mechanisms and functions," in *The Development of Autobiographical Reasoning in Adolescence and Beyond. New Directions in Child and Adolescent Development*, ed. T. Habermas (San Francisco: Jossey-Bass), 131, 1–17.

Habermas, T., and Berger, N. (2011). Retelling everyday emotional events: condensation, distancing, and closure. *Cogn. Emot.* 25, 206–219. doi:10.1080/02699931003783568

Habermas, T., and Bluck, S. (2000). Getting a life: the development of the life story in adolescence. *Psychol. Bull.* 126, 748–769. doi:10.1037/0033-2909.126.5.748

Habermas, T., and de Silveira, C. (2008). The development of global coherence in life narratives across adolescence: temporal, causal, and thematic aspects. *Dev. Psychol.* 44, 707–721. doi:10.1037/0012-1649.44.3.707

Habermas, T., and Diel, V. (2010). The emotional impact of loss narratives: event severity and narrative perspectives. *Emotion* 10, 312–323. doi:10.1037/a0018001

Habermas, T., Diel, V., and Welzer, H. (in press). Lifespan trends of autobiographical remembering: episodicity and search for meaning. *Conscious. Cogn.*

Habermas, T., Ehlert-Lerche, S., and de Silveira, C. (2009a). The development of the temporal macrostructure of life narratives across adolescence: beginnings, linear narrative form, and endings. *J. Pers.* 77, 527–560. doi:10.1111/j.1467-6494.2008.00557.x

Habermas, T., Meier, M., and Mukhtar, B. (2009b). Are specific emotions narrated differently? *Emotion* 9, 751–762. doi:10.1037/a0018002

Habermas, T., and Köber, C. (in press). "Autobiographical reasoning is constitutive for narrative identity: the role of the life story for personal continuity," in *The Oxford Handbook of Identity Development*, eds K. C. McLean and M. Syed (Oxford: Oxford University Press).

Habermas, T., Negele, A., and Brenneisen Mayer, F. (2010). Honey, you're jumping about – mothers' scaffolding of their children's and adolescents' life narration. *Cogn. Dev.* 25, 339–351. doi:10.1016/j.cogdev.2010.08.004

Habermas, T., Ott, L. M., Schubert, M., Schneider, B., and Pate, A. (2008). Stuck in the past: negative bias, explanatory style, temporal order, and evaluative perspectives in life narratives of clinically depressed individuals. *Depress. Anxiety* 25, E121–E132. doi:10.1002/da.20389

Hemphill, J. F. (2003). Interpreting the magnitudes of correlation coefficients. *Am. Psychol.* 58, 78–80. doi:10.1037/0003-066X.58.1.78

Kopelman, M. D., Wilson, B. A., and Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.* 11, 724–744. doi:10.1080/01688638908400928

Labov, W., and Waletzky, J. (1967). "Narrative analysis: oral versions of personal experience," in *Essays on the Verbal and Visual Arts. Proceedings of the 1966 Annual Spring Meeting of the American Ethnological Society*, ed. I. Helm (Seattle, WA: University of Washington Press), 12–44.

Levine, B., Svoboda, E., Hay, J. F., Winocur, W., and Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic memory. *Psychol. Aging* 17, 677–689. doi:10.1037/0882-7974.17.4.677

Lilgendahl, J. P., and McAdams, D. P. (2011). Constructing stories of self-growth: how individual differences in patters of autobiographical reasoning relate to well-being. *J. Pers.* 779, 391–428. doi:10.1111/j.1467-6494.2010.00688.x

Linde, C. (1993). *Life Stories*. Oxford: Oxford University Press.

Markowitsch, H. J., and Staniloiu, A. (2011). Memory, consciousness, and the self. *Conscious. Cogn.* 20, 16–39. doi:10.1016/j.concog.2010.09.005

McAdams, D. P. (2006). *The Redemptive Self*. Oxford: Oxford University Press.

Neisser, U. (1982). *Memory Observed: Remembering in Natural Contexts.* New York: Freeman.

Neisser, U. (1986). "The nested structure of autobiographical memory," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 71–81.

Nelson, K., and Fivush, R. (2004). The emergence of autobiographical memory: a social cultural developmental theory. *Psychol. Rev.* 111, 486–511. doi:10.1037/0033-295X.111.2.486

Nelson, K. L., Moskovitz, D. J., and Steiner, H. (2008). Narration and vividness as measures of event-specificity in autobiographical memory. *Discourse Process.* 45, 195–209. doi:10.1080/01638530701792891

Piolino, P., Desgranges, B., and Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314–2329. doi:10.1016/j.neuropsychologia.2009.01.020

Robinson, J. A. (1986). "Autobiographical memory: a historical prologue," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 9–24.

Rosenbaum, S., Gilboa, A., Levine, B., Winocur, G., and Moscovitch, M. (2009). Amnesia as an impairment of detail generation and binding: evidence from personal, fictional, and semantic narratives in K. C. *Neuropsychologia* 47, 2181–2187. doi:10.1016/j.neuropsychologia.2008.11.028

Rosenthal, G. (1995). *Erlebte und Erzählte Lebensgeschichte [The Lived and Narrated Life Story]*. Frankfurt: Campus.

Rubin, D. C., Berntsen, D., and Bohni, M. K. (2008). A memory-based model of posttraumatic stress disorder: evaluating basic assumptions underlying the PTSD diagnosis. *Psychol. Rev.* 115, 985–1011. doi:10.1037/a0013397

Rubin, D. C., Wetzler, S. E., and Nebes, R. D. (1986). "Autobiographical memory across the life span," in *Autobiographical Memory*, ed. D. C. Rubin (Cambridge: Cambridge University Press), 202–221.

Sumner, J. A., Mineka, S., and McAdams, D. P. (2013). Specificity in autobiographical narratives correlates with performance on the Autobiographical Memory Test and prospectively predicts depressive symptoms. *Memory* 21, 646–656. doi:10.1080/09658211.2012.746372

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York: Academic Press), 381–402.

Tulving, E. (1983). *Elements of Episodic Memory*. New York: Oxford University Press.

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12. doi:10.1037/h0080017

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Waters, T., Bauer, P., and Fivush, R. (2013). *Autobiographical Memory Functions, Served by Multiple Event Types.* Unpublished manuscript, Department of Psychology, Emory University, Atlanta, GA.

Wheeler, M. A., Stuss, D. T., and Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychol. Bull.* 121, 331–354. doi:10.1037/0033-2909.121.3.331

Williams, J. M. G., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., et al. (2007). Autobiographical memory specificity and emotional disorder. *Psychol. Bull.* 133, 122–148. doi:10.1037/0033-2909.133.1.122

Willoughby, K. A., Desrocher, M., Levine, B., and Rovet, J. F. (2012). Episodic and semantic autobiographical memory and everyday memory during late childhood and early adolescence. *Front. Psychol.* 3:53. doi:10.3389/fpsyg.2012.00053

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APPENDIX

MALE PARTICIPANT, 8 YEARS, TOTAL OF SIX SEGMENTS, SEGMENT 6 "FLEA MARKET"

"Now I have to think what else. There was a flea market now. That was very exciting. That was fun. I sold some stuff."

Ratings: vividness 2, detailedness – person 0, place 1, time 2, specific memory, chronicle, emotion 3, interpretation 1, life story integration 0, valence 1, 0 months old memory, 5 propositions.

MALE PARTICIPANT, 20 YEARS, TOTAL OF 22 SEGMENTS, SEGMENT 21 "FATHER DOESN'T KNOW EVERYTHING"

"But already in 7th grade I started asking questions, which my father couldn't give an answer to, and then it was "I don't know it". But then I was thinking by myself, "Why, why doesn't he know it?" I mean, that's when I first noticed, that my father doesn't know everything, that he is also only human, that he is a real normal person. Before then it was always like, my Dad is my big role model."

Ratings: vividness 3, detailedness – person 2, place 0, time 1, extended memory, narrative, emotion 0, interpretation 2, life story integration 1, valence 2, 103 months old memory, 13 propositions.

FEMALE PARTICIPANT, 60 YEARS, 37 SEGMENTS, SEGMENT 24 "FATHER REMARRIES"

"That year my father married for a second time. And that was quite incisive because he totally focussed on his new wife and family, such that I – had done my part, and we have no contact till today. I can't accept letting myself be hurt anymore. It was like, he was like totally changed, as if what I did, didn't count for anything anymore, I had passed my youth, my early adulthood, when other women start a family of their own, I spent that time with my father. Therefore for me it was like he gave me a kick. We had been very close, almost like a couple without sex. We had even been addressed as husband and wife. And then he just remarried, very fast after my mother had died, which I could not understand. But well, that's the way it went."

Ratings:, vividness 2, detailedness – person 1, place 0, time 1, specific memory, argument, emotion 2, interpretation 2, life story integration 2, valence −1, 326 months old memory, 21 propositions.

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Self-serving episodic memory biases: findings in the repressive coping style

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Individuals with a repressive coping style self-report low anxiety, but show high defensiveness and high physiological arousal. Repressors have impoverished negative autobiographical memories and are better able to suppress memory for negatively valenced and self-related laboratory materials when asked to do so. Research on spontaneous forgetting of negative information in repressors suggests that they show significant forgetting of negative items, but only after a delay. Unknown is whether increased forgetting after a delay is potentiated by self-relevance. Here we asked in three experiments whether repressors would show reduced episodic memories for negative self-relevant information when tested immediately versus after a 2-day delay. We predicted that repressors would show an exaggerated reduction in recall of negative self-relevant memories after a delay, at least without anew priming of this information. We tested a total of 300 participants (experiment 1: $N = 95$, experiment 2: $N = 106$; experiment 3: $N = 99$) of four types: repressors, high-anxious (HA), low-anxious, and defensive HA individuals. Participants judged positive and negative adjectives with regard to self-descriptiveness, serving as incidental encoding. Surprise free-recall was conducted immediately after encoding (experiment 1), after a 2-day delay (experiment 2), or after a 2-day delay following priming via a lexical decision task (experiment 3). In experiment 1, repressors showed a bias against negative self-relevant words in immediate recall. Such a bias was neither observed in delayed recall without priming nor in delayed recall with priming. Thus, counter to our hypothesis, negative information that was initially judged as self-relevant was not forgotten at a higher rate after a delay in repressors. We suggest that repressors may reinterpret initially negative information in a more positive light after a delay, and therefore no longer experience the need to bias their recall after a delay.

Keywords: memory, repressive coping style, self-relevance, delay, valence

INTRODUCTION

Repression is a putative psychological defense mechanism (Freud, 1957/1915) that inhibits anxiety-provoking, ego-threatening thoughts from entering consciousness. Debated for over a century, there has been little empirical evidence for the existence of repression, either as a trauma-specific or a general mechanism of forgetting (Erdelyi, 2006). An alternative is to measure differences between individuals' repressive tendencies. The most studied approach by Weinberger et al. (1979) defines "repressors" as individuals who score high on self-report measures of defensiveness and low in measures of trait-anxiety. Thus, scores in two questionnaires are combined, trait-anxiety and trait-defensiveness. As a consequence, three additional groups of individuals are identified: "Low-anxious (LA)" individuals score low in trait-anxiety and low in trait-defensiveness. These are thought to be people with "truly" low anxiety since they do not respond defensively in questionnaires, unlike repressors. "High-anxious (HA)" individuals score low in defensiveness but high in trait-anxiety; and "defensive HA" individuals have high scores on both scales. A crucial finding is that repressors exhibit physiologically high levels of anxiety-related arousal despite their low self-reported anxiety (Weinberger et al., 1979; Broomfield and Turpin, 2005). Thus, by this operational definition, repressors have high levels of unacknowledged anxiety. Importantly, repressive coping style has been associated with deleterious effects on physical well-being, most consistently an increased risk for hypertension, cardiovascular diseases, and cancer (Mund and Mitte, 2012).

The motivation to maintain a positive self-view and avoid the experience of anxiety may drive repressors more than others to truncate, inhibit, or otherwise alter negative information processing. Indeed, repressors show biases against processing negative information. For example, compared to non-repressors, repressors recall fewer and less detailed negative autobiographical memories (e.g., Davis and Schwartz, 1987; Davis, 1990; Dickson et al., 2009; Geraerts et al., 2012). When directly instructed to inhibit processing of negative information, repressors are superior to

non-repressors in (negative) thought suppression (Barnier et al., 2004; Geraerts et al., 2006, 2007). Repressors' superior inhibition of negative information has also been shown in memory. For example, repressors had increased forgetting of negative self-related materials in list-method directed forgetting paradigms (Myers et al., 1998; Myers and Derakshan, 2004). They were also better able to perform the think/no-think task (Anderson and Green, 2001) than non-repressors, at least when they were given positive target memories to recall instead of negative ones (Hertel and McDaniel, 2010). Thus, active inhibition of negative, and especially, self-relevant memories may play a role in repressors' selective forgetting of information in experimental contexts in which they are told to forget.

Repressors' naturally occurring, uninstructed forgetting of laboratory materials has been more variable. Brosschot et al. (1997) found nothing remarkable about repressors' free-recall and recognition of unpleasant (and pleasant) words. Similarly, Oldenburg et al. (2002) found neither implicit nor explicit memory biases against negative materials in repressors. Avero et al. (2003) found that individuals with an avoidant coping style (similar to the repressive coping style) had a more conservative response bias (β) but intact recognition sensitivity (d-prime) in recognition memory for negative words than other people. That is, repressors compared to non-repressors judged negative words (both target words and lure words) less often as "old items" in a recognition memory test, even though their ability to differentiate successfully between negative target words and negative lure words was intact. Focussing on self-related information rather than just valenced materials, Saunders et al. (2012) found in a series of studies that repressors are most susceptible to the mnemic neglect effect (Green and Sedikides, 2004; Green et al., 2008) compared to individuals with other coping styles. In mnemic neglect studies, participants are exposed to hypothetical scenarios that involve either themselves or a different person. These scenarios imply favorable or unfavorable personality traits (e.g., "I would keep secrets when asked to") with different importance to people's self-concept and different modifiability. In general, a "mnemic neglect" is reflected in reduced recall of situations that involve the self, and unfavorable, personally important, and unmodifiable characteristics. Repressors in Saunders et al. (2012) showed the strongest such mnemic neglect effects in a series of three experiments. Thus, personal involvement or significance, in addition to negative valence might be important to evoke spontaneous, i.e., unprovoked, memory biases in repressive individuals.

Hock, Krohne, and colleagues (Hock and Krohne, 2004; Krohne and Hock, 2008, 2011; Peters et al., 2012) define and measure repressive coping style using the Mainz Coping Inventory (MCI: Krohne and Egloff, 1989; Krohne et al., 2000). The MCI does not rely on the combination of defensiveness and anxiety but incorporates individual differences in information processing styles. MCI-repressors are thought to be motivated to control their experience of anxiety-related arousal and characterized by high dispositional threat avoidance. Their most extreme counterpart, sensitizers, are thought to be motivated to control potential dangers resulting from fearful situations. Therefore, MCI-based sensitizers are thought to be uncertainty-oriented and show high dispositional threat vigilance. Using this operationalization, repressors were found to show no biases against threat-related information in immediate retrieval (recognition memory for negative words/sentences or pictures), but those biases emerged only when testing was delayed by three days (Hock and Krohne, 2004; Krohne and Hock, 2008; see also Peters et al., 2012). This pattern has also been termed *repressive discontinuity hypothesis* indicating that repressors may have an early attentional bias toward threat but selectively retain non-threat and forget threat-information later on (Calvo and Eysenck, 2000; Caldwell and Newman, 2005; Derakshan et al., 2007; Paul et al., 2012). Krohne and Hock (2011) suggested based on the schema pointer plus tag model of Graesser and Bower (1990) that retrieval may co-vary with the level of atypicality of memories. According to this model, schema-incongruent information is better recalled at immediate testing and schema-congruent information is better recalled at delayed testing. If repressors have fewer threat-schemata than non-repressors, they should effectively retrieve threat-information immediately, but have reduced recall of (schema-incongruent) threat-related information at a delayed test. This is consistent with their findings (Hock and Krohne, 2004; Krohne and Hock, 2008; Peters et al., 2012).

If the main motivation of a repressive coping style is self-protection, one would expect to see decreased memory predominantly in tasks that require relating negative thoughts and memories to oneself (Myers and Derakshan, 2004; Saunders et al., 2012). Consequently, it seems likely that differences in personal involvement evoked by particular tasks may have contributed to the variability of the aforementioned results. For instance, the null findings of Brosschot et al. (1997) may have been due to participants simply rating stimuli for pleasantness and threat, a task that can be performed with minimal reference to oneself. Along this line, Fujiwara et al. (2008) also found no alterations in repressors' recall or priming for negative information they had judged for valence. In contrast, within the same study, self-descriptiveness judgments critically mediated forgetting in repressors: non-repressors had better free-recall of negative self-descriptive words compared to negative non-self-descriptive words. In contrast, repressors showed no such free-recall benefit for negative self-descriptive information. Despite these group differences in free-recall, implicit memory (priming) for negative self-descriptive information was similar across groups. Thus, self-descriptiveness mediated free-recall (but not priming) biases against negative information even at an immediate test in our previous study. However, unknown is whether such self-serving rather than just valence-driven bias would become stronger over time.

Thus, we compared here whether repressive coping style mediated free-recall of words previously judged as self-descriptive at an immediate test (conceptual replication of Fujiwara et al., 2008), and at a delayed test. First, we expected to replicate our previous result and predicted that all groups but repressors should show a recall advantage of negative self-descriptive over negative information that was not self-descriptive in immediate test (experiment 1). Secondly, we expected that these immediate biases would become more pronounced with a delay (experiment 2). Thus, if schema-congruency drives delayed retrieval more so than immediate retrieval and repressors possess fewer negative self-schemata than non-repressors, repressors may retrieve even less

negative self-descriptive information after a delay than immediately. Finally, we tested whether potential recall biases at delayed testing could be influenced by cueing all original materials prior to free-recall using a lexical decision task (experiment 3). Based on autobiographical memory work by Davis and others (Davis and Schwartz, 1987; Davis, 1990), who showed that repressors can be cued to retrieve negative autobiographical information that they did not report otherwise, we expected that repressors may not show conceivable biases against recalling negative self-descriptive information if they had been cued immediately prior to free-recall at the delayed test. We did not expect repressor-specific alterations of implicit memory in the lexical decision task after the delay. As we reported previously (Fujiwara et al., 2008), priming for negative self-relevant information had been intact in repressors at immediate test, and we did not expect this to change after a delay.

MATERIALS AND METHODS

PARTICIPANTS

Participants were a total of 351 introductory psychology students at the University of Alberta. Participants gave written informed consent prior to the study, which was approved by a University of Alberta Research Ethics Board. In online mass-testing sessions at the beginning of fall and winter semesters between 2007 and 2010, all students enrolled in an introductory psychology course (between 1500 and 2500 students in each fall/winter term) completed the Trait-version of the State-Trait-Anxiety Inventory (STAI-T; Spielberger et al., 1983) and the Self-Deceptive Enhancement (SDE) component of the Balanced Inventory of Desirable Responding scale (BIDR; Paulhus, 1991), in this fixed order. The STAI-T consists of 24-point scaled statements measuring trait-anxiety (maximum score: 80). The BIDR-SDE consists of 27-point scaled statements that measure self-deceptive aspects of social desirability, such as beliefs of invincibility and exaggerated optimism (maximum score: 140). Only native English speakers with complete questionnaire and demographic data as well as below 30 years of age were included. Participants were categorized into four coping styles according to Weinberger's classification scheme (Weinberger et al., 1979) based on quartile splits of BIDR-SDE scores (cut-off: 74 and 92 points, for lowest and highest quartile respectively) and median splits on STAI-T scores (43 points) of the 1539 eligible students tested in the 2007 fall semester. Subsequent semesters used the same cut-off scores to ensure consistency across samples. Participants in each semester were classified as repressors (REP: low-anxious, high-defensive), truly low-anxious (LA: low-anxious, low-defensive), truly high-anxious (HA: high-anxious, low-defensive), and defensive high-anxious (DHA: high-anxious, high-defensive). Based on the BIDR-SDE and STAI-T cut-off scores, a first enrolment wave in each semester allowed equally sized groups of participants with one of the four coping styles online access to self-enroll in the experiments. The size of the groups that received access to the experiment was determined by the maximum number of participants in the smallest of the four groups (usually, the DHA). Additional enrolment waves were initiated when participation rates started to decline usually around midway through the semesters, giving more participants access to the experiment. These participants were usually more REP and HA as these two groups were more common than LA and especially than DHA. Students were not aware of the nature of the experiment at the time of self-enrolment and testers were not aware of the participants' coping style at the time of the experiment. In experiment 1, 99 students participated, 122 students participated in experiment 2, and 130 in experiment 3. Data from 52 participants were excluded: 22 had partial data or otherwise did not comply with the task instructions (e.g., less than 50% valid trials, less than two words in free-recall), 19 did not return after the delay to complete the experiment, 3 experienced a computer error, and 8 participants' pre-selection questionnaire data were erroneous.

The final sample in experiment 1 included 95 participants. A total of 22 (15 female) LA, 26 (13 female) HA, 28 (14 female) REP, and 19 (11 female) DHA individuals participated, with an average age of 20.02 ± 1.77 years. Gender was equally distributed across groups [$\chi^2(3) = 2.14$, $p > 0.1$]. The final sample in experiment 2 included 106 participants. A total of 26 (21 female) LA, 26 (16 female) HA, 31 (14 female) REP, and 23 (14 female) DHA individuals participated, with an average age of 19.00 ± 1.66 years. Although there were slightly more female participants in the LA group than in the other groups, the gender distribution was not statistically different across all groups [$\chi^2(3) = 7.56$, $p > 0.05$]. Finally, experiment 3 included 99 participants. A total of 27 (16 female) LA, 28 (16 female) HA, 23 (10 female) REP, and 21 (14 female) DHA individuals participated, with an average age of 18.86 ± 1.93 years. Gender was equally distributed across groups [$\chi^2(3) = 2.56$, $p > 0.1$]. Participants' questionnaire data are summarized in **Table 1**.

As intended, in each experiment, anxiety (STAI-T) was significantly different across groups [experiment 1: $F(3, 91) = 75.97$; experiment 2: $F(3, 102) = 61.54$; experiment 3: $F(3, 95) = 89.91$, all p's < 0.001], and so was defensiveness (BIDR-SDE) [experiment 1: $F(3, 91) = 292.81$; experiment 2: $F(3, 104) = 187$;

Table 1 | Means (*M*) and standard deviations (SD) of questionnaire data across groups in all three experiments.

	LA		HA		REP		DHA	
	M	**SD**	***M***	**SD**	***M***	**SD**	***M***	**SD**
EXPERIMENT 1								
STAI-T	36.00^a	2.88	53.00^b	7.52	35.14^a	3.58	51.47^b	6.50
BIDR-SDE	69.90^c	3.94	68.65^c	4.76	99.04^d	5.20	96.42^d	4.85
EXPERIMENT 2								
STAI-T	38.88^a	3.51	50.92^b	6.51	37.35^a	2.20	48.13^b	4.78
BIDR-SDE	70.87^c	4.12	69.34^c	8.09	96.42^d	5.30	94.09^d	3.06
EXPERIMENT 3								
STAI-T	37.85^a	3.03	48.82^b	3.57	35.13^a	2.69	48.05^b	5.12
BIDR-SDE	70.85^c	3.31	68.86^c	4.45	98.82^d	7.06	95.19^d	4.24

STAI-T, trait-version of the State-Trait-Anxiety Inventory (Spielberger et al., 1983); BIDR-SDE, self-deceptive enhancement scale of the Balanced Inventory of Desirable Responding (Paulhus, 1991); LA, low-anxious; HA, high-anxious; REP, repressor; DHA, defensive high-anxious. Cells with different superscripts show significant between-group differences within each experiment, indicated by post hoc Scheffé test ($p < 0.001$).

experiment 3: $F(3, 95) = 255.26$, all p's < 0.001]. *Post hoc* Scheffé tests indicated higher anxiety in HA/DHA than in LA/REP groups, but no differences between groups with high anxiety scores (HA, DHA), or between groups with low anxiety scores (LA, REP). Likewise, defensiveness was always substantially higher in groups intended to have high defensiveness (REP, DHA) than in those with low-defensiveness (LA, HA), but never differed between REP and DHA or between LA and HA (all p's < 0.001).

MATERIALS AND TASKS

Stimuli were personality trait words drawn from Anderson (1968). Based on median splits of likeableness, we created two matched sets, each with 75 likeable and 75 non-likeable words (hereafter termed "positive" and "negative," respectively). Sets were equated in word length (3–10 letters), statistical frequency, and meaningfulness (for details see Fujiwara et al., 2008). Half the participants in each experiment received set 1 or set 2 during the encoding task. The unused words (i.e., either set 1 or set 2, depending on its use in the encoding task) were included in experiment 3 as new words in the lexical decision task. The fixed task order was as follows: experiment 1: self-referential judgments, free-recall. Experiment 2: self-referential judgments, 2-day delay, free-recall. Experiment 3: self-referential judgments, 2-day delay, lexical decision task, free-recall.

Encoding task

Participants were presented with 150 personality trait words (75 positive, 75 negative). Participants were asked to judge how descriptive each word was of themselves, on a four-point scale: "1" = very self-descriptive, "2" = moderately self-descriptive, "3" = moderately not-self-descriptive, and "4" = not at all self-descriptive. In each trial, a fixation cross appeared for 500 ms, followed by a centrally presented word (3000 ms) at which time participants would make their self-descriptiveness rating. Six practice trials were given. Eight filler words were presented at the end of the task to avoid recency effects. Practice and filler words were excluded from the analyses. Dependent variables were the proportions of word judgments, summarized into composite measures described in more detail in Section "Statistical Analyses."

Free-recall

Participants were given 5 minutes to write on a piece of paper in any order as many words as they could recall from the encoding task. The dependent variable was the proportion of words recalled.

Lexical decision task (experiment 3 only)

Participants were presented the 150 words they had judged in the encoding task, 150 new words (either word set 1 or set 2, see above), as well as 300 pronounceable non-word letter strings. Participants were asked to judge each letter string as a word or a non-word. Speed and accuracy were emphasized equally. Practice trials contained six words and three non-words. None of them were included in the experiment. Each trial had the following sequence: a fixation cross would appear for 1000 ms followed by a 150-ms presentation of the letter string, after which the participant had to respond (identical to Fujiwara et al., 2008). The dependent variable was response time.

Except for free-recall, tasks were administered using Presentation software (www.neurobs.com) on laptop computers. Stimuli were presented in light gray, 36-point Arial font in the center of a black screen. All three experiments were conducted in small groups of one to three participants at a time. Participants were facing opposite walls to prevent them from watching each other perform the tasks.

Statistical analyses

To avoid empty cells, self-descriptiveness judgments were collapsed from four into two response categories. The judgments "very self-descriptive" and "moderately self-descriptive" were coded together as "self-descriptive"; "moderately not-self-descriptive" and "not at all self-descriptive" judgments were coded as "not-self-descriptive."

As self-referential judgments are mutually exclusive (each word can be judged as either self-descriptive or not, but not both), we derived two composite measures to illustrate performance in the encoding task. First, we calculated a "self-judgment ratio" by dividing the proportion of all words judged as self-descriptive by proportions of words judged as not-self-descriptive, and subsequently log-transforming this ratio to make the distribution symmetric. Positive scores indicate more self-descriptive than not-self-descriptive judgments, regardless of valence. Secondly, we calculated a "positivity-judgment ratio" by dividing the proportion of favorable judgments (negative not-self-descriptive judgments and positive self-descriptive judgments) by the proportion of unfavorable judgments (negative self-descriptive judgments and positive not-self-descriptive judgments), and log-transforming this ratio. Positive scores indicate more favorable self-judgments than unfavorable self-judgments. The two ratios were compared with univariate ANOVA and between-subject factors anxiety (low/high) and defensiveness (low/high), separately for all three experiments. Splitting up the two components comprising the coping styles (anxiety, defensiveness) allowed us to investigate whether the interaction of anxiety and defensiveness (i.e., the repressive coping style) influenced our results over and above anxiety or defensiveness alone[1]. Free-recall and priming effects were analyzed with mixed repeated-measures ANOVA separately for each of the three experiments, consistent with our previous study (Fujiwara et al., 2008). Performance was calculated as proportions of words identified in priming or recalled in free-recall relative to each individual's total number of negative and positive self-descriptive or not-self-descriptive words from the prior judgment task (possible maximum of 75 negative and 75 positive words). Thus, the dependent variables: proportional recall and priming were analyzed as a function of within-subject factors valence (positive/negative) and prior self-judgment from the encoding task (self-descriptive/not-self-descriptive).

[1]The grouping of individuals into one of the four coping styles (LA, HA, REP, DHA) using distinct cut-off scores based on the underlying sample is a somewhat arbitrary approach that has been criticized. Employing a combined score of defensiveness and anxiety (cf. Mendolia, 2002) can circumvent this issue and reanalysis of our results with such index score and hierarchical regression analyses did not qualitatively change our results, but lowered statistical power in some of the analyses. For reasons of clarity and to allow comparison with previous studies, we present our results in the more conventional categorical fashion.

Between-subject factors were anxiety (low/high) and defensiveness (low/high).

To control for possible influences of individual compared to small group testing conditions, we included presence/absence of other participants at encoding or free-recall as a dummy-coded categorical covariate in all analyses.

Responses faster than 200 ms or three standard deviations above or below an individual's mean response time were excluded from all analyses. In the lexical decision task, priming was measured as the amount of time required to identify new words minus the time required to identify old words. Collapsed across factor levels, all dependent variables were normally distributed, assessed with Kolmogorov–Smirnov tests. Our statistical significance level was set to $p < 0.05$.

RESULTS

ENCODING TASK

Table 2 gives an overview on the encoding task results across all three experiments.

As can be seen in **Table 2**, participants on average judged slightly more than 50% of all words as self-descriptive and about 70% of their judgments were favorable. The self-judgment ratio was above zero in all experiments [experiment 1: $t(94) = 4.2$, $p < 0.001$, Cohen's $d = 0.9$; experiment 2: $t(105) = 2.01$, $p < 0.05$, $d = 0.4$; experiment 3: $t(98) = 2.95$, $p < 0.01$, $d = 0.6$], indicating more self-descriptive than not-self-descriptive judgments. Controlling for presence/absence of other participants during the experiment [experiment 1: $F(1, 90) = 0.003$, $p > 0.1$, $\eta_{partial}^2 < 0.0001$; experiment 2: $F(1, 101) = 0.74$, $p > 0.1$, $\eta_{partial}^2 = 0.007$; experiment 3: $F(1, 94) = 0.14$, $p > 0.1$, $\eta_{partial}^2 = 0.001$], this ratio was not influenced by groupings of anxiety, defensiveness, or their interaction in experiments 1 and 3 (all p's > 0.1; all $\eta_{partial}^2 < 0.02$). However, anxiety grouping did show a main effect in experiment 2 [$F(1, 101) = 7.38$, $p < 0.01$, $\eta_{partial}^2 = 0.07$] indicating more self-judgments than not-self-judgments in higher anxious groups. There was no main effect of defensiveness [$F(1, 101) = 0.08$, $p > .1$, $\eta_{partial}^2 = 0.001$] on the self-judgment ratio and neither an interaction between anxiety and defensiveness [$F(1, 101) = 0.30$, $p > 0.1$, $\eta_{partial}^2 < 0.003$]. Thus, all participants tended to make more self-descriptive than not-self-descriptive judgments in all experiments, although this tendency was attenuated in individuals with lower anxiety in experiment 2.

The positivity-judgment ratio was substantially above zero in all experiments [experiment 1: $t(94) = 17.21$, $p < 0.001$, $d = 3.55$; experiment 2: $t(105) = 17.49$, $p < 0.001$, $d = 3.41$; experiment 3: $t(98) = 18.37$, $p < 0.001$, $d = 3.71$], indicating more favorable than unfavorable judgments in general. Controlling for presence/absence of other participants during the experiment [experiment 1: $F(1, 90) = 1.64$, $p > 0.1$, $\eta_{partial}^2 = 0.02$; experiment 2: $F(1, 101) = 0.18$, $p > 0.1$, $\eta_{partial}^2 = 0.002$; experiment 3: $F(1, 94) = 0.96$, $p > 0.1$, $\eta_{partial}^2 = 0.01$], the positivity-judgment ratio differed significantly across groups. Defensiveness showed main effects in all three experiments [experiment 1: $F(1, 90) = 11.9$, $p < 0.001$, $\eta_{partial}^2 = 0.12$; experiment 2: $F(1, 101) = 8.15$, $p < 0.01$, $\eta_{partial}^2 = 0.08$; experiment 3: $F(1, 94) = 10.29$, $p < 0.01$, $\eta_{partial}^2 = 0.1$], indicating more self-positive judgments in individuals with high defensiveness than in low-defensive individuals. In addition, anxiety showed a main effect in experiment 2 only [experiment 2: $F(1, 101) = 20.0$, $p < 0.001$, $\eta_{partial}^2 = 0.17$] with a less pronounced positivity-judgment ratio in high compared to low anxiety groups. A significant interaction between anxiety and defensiveness grouping was observed in experiment 1 [$F(1, 90) = 7.53$, $p < 0.01$, $\eta_{partial}^2 = 0.08$]. Following up on this interaction, comparing all four separate groups with a one-way ANOVA [$F(3, 91) = 7.2$, $p < 0.001$] and *post hoc* Scheffé tests showed a significantly higher positivity-judgment ratio in the REP group than in the LA group. While present in similar but weaker form, the interaction did not reach significance in experiment 2 [$F(1, 101) = 2.05$, $p > 0.1$, $\eta_{partial}^2 = 0.02$] or experiment 3 [$F(1, 94) = 3.18$, $p < 0.1$, $\eta_{partial}^2 = 0.033$].

In summary, while all four groups showed a sizable preference to make favorable self-judgments (endorsing positive words as self-descriptive and rejecting negative words as not-self-descriptive), this preference was reliably increased in higher defensive participants across all experiments; and attenuated in individuals with higher anxiety in experiment 2 only. In REP, this tendency had a similar size across experiments and was, numerically, the largest of each of the four groups in all experiments.

FREE-RECALL

Conditional on the self-descriptiveness judgments from the encoding task, we then analyzed the proportions of words retrieved in free-recall in each of the experiments, as a function of within-subjects factors valence (positive/negative) and prior self-judgment from the encoding task (self-descriptive/not-self-descriptive), and between-subject factors anxiety (low/high) and defensiveness (low/high), again, controlling for presence/absence of other participants during the experiment. Means and standard deviations of proportional free-recall are shown in **Table 3**.

In experiment 1 (immediate recall), controlling for the covariate "presence/absence of other participants during the experiment," we observed a main effect of self-judgment [$F(1, 90) = 10.10$, $p < 0.01$, $\eta_{partial}^2 = 0.1$], indicating better recall of words that were previously judged as self-descriptive than words that were judged as not-self-descriptive. Furthermore, we observed a four-way interaction between valence, self-judgment, anxiety, and defensiveness, just reaching significance [$F(1, 90) = 4.23$, $p < 0.05$, $\eta_{partial}^2 = 0.05$]. To follow up on this interaction, we first compared all four recall proportions across groups with four one-way ANOVA. These were not significant [negative self-descriptive: $F(1, 91) = 1.56$, $p = 0.21$; negative not-self-descriptive: $F(1, 91) = 0.48$, $p = 0.7$; positive self-descriptive: $F(1, 91) = 0.72$, $p = 0.55$; positive not-self-descriptive: $F(1, 91) = 0.43$, $p = 0.73$]. Secondly, we conducted mixed repeated-measures ANOVA within each of the four groups. Due to small cell sizes the covariate was omitted for these analyses. We observed main effects of self-judgment in LA [$F(1, 21) = 9.5$, $p < 0.01$, $\eta_{partial}^2 = 0.31$], HA [$F(1, 25) = 17.37$, $p < 0.001$, $\eta_{partial}^2 = 0.41$], and DHA [$F(1, 18) = 8.2$, $p < 0.01$, $\eta_{partial}^2 = 0.31$], indicating better recall of self-descriptive than not-descriptive information. This main effect was not present in REP [$F(1, 27) = 1.07$, $p = 0.39$, $\eta_{partial}^2 = 0.038$]. Finally, dependent-samples t-tests were conducted within each group (see **Figure 1A** for an illustration of

Table 2 | Means (*M*) and standard deviations (SD) of judgment proportions (out of 150 words) in the encoding task.

	LA		HA		REP		DHA		Total	
	M	**SD**	***M***	**SD**	***M***	**SD**	***M***	**SD**	***M***	**SD**
EXPERIMENT 1										
Self	0.49	0.08	0.51	0.06	0.51	0.06	0.53	0.06	0.51	0.07
Not-self	0.47	0.08	0.44	0.07	0.45	0.06	0.44	0.06	0.45	0.07
Self-negativity	0.32	0.13	0.27	0.11	0.19	0.07	0.26	0.10	0.26	0.11
Self-positivity	0.63	0.14	0.69	0.10	0.77	0.07	0.71	0.10	0.71	0.12
Self-judgment ratio	0.06	0.35	0.14	0.29	0.12	0.23	0.17	0.24	0.12	0.28
Self-positivity ratio	0.72	0.68	1.02	0.55	1.45	0.45	1.08	0.58	1.09	0.12
EXPERIMENT 2										
Self	0.48	0.07	0.52	0.09	0.49	0.06	0.52	0.07	0.50	0.08
Not-self	0.48	0.08	0.44	0.10	0.48	0.06	0.46	0.09	0.47	0.08
Self-negativity	0.27	0.05	0.33	0.12	0.20	0.09	0.30	0.12	0.27	0.11
Self-positivity	0.69	0.08	0.63	0.12	0.76	0.08	0.67	0.12	0.69	0.11
Self-judgment ratio	−0.01	0.32	0.18	0.42	0.02	0.27	0.13	0.34	0.07	0.34
Self-positivity ratio	0.99	0.42	0.68	0.56	1.41	0.55	0.83	0.58	1.01	0.60
EXPERIMENT 3										
Self	0.49	0.07	0.52	0.08	0.50	0.08	0.50	0.08	0.51	0.08
Not-self	0.47	0.07	0.45	0.09	0.46	0.09	0.46	0.09	0.46	0.08
Self-negativity	0.29	0.11	0.28	0.09	0.20	0.10	0.25	0.08	0.26	0.10
Self-positivity	0.67	0.12	0.69	0.09	0.76	0.11	0.71	0.09	0.71	0.11
Self-judgment ratio	0.06	0.31	0.16	0.35	0.10	0.40	0.09	0.35	0.10	0.35
Self-positivity ratio	0.87	0.60	0.95	0.47	1.42	0.63	1.10	0.48	1.07	0.58

Self: self-descriptive judgments; Not-self: not-self-descriptive judgments; Self-positivity: positive self-descriptive and negative not-self-descriptive judgments; Self-negativity: positive not-self-descriptive and negative self-descriptive judgments; Self-judgment ratio: log-transformed self/not-self; Self-positivity ratio: log-transformed self-positivity/self-negativity. LA, low-anxious; HA, high-anxious; REP, repressor; DHA, defensive high-anxious.

Table 3 | Means (*M*) and standard deviations (SD) of recall proportions of words as they had been judged in encoding.

	LA		HA		REP		DHA		Total	
	M	**SD**	***M***	**SD**	***M***	**SD**	***M***	**SD**	***M***	**SD**
EXPERIMENT 1										
Negative self	0.16	0.09	0.14	0.10	0.11	0.10	0.17	0.09	0.14	0.10
Negative not-self	0.10	0.05	0.10	0.05	0.10	0.05	0.11	0.05	0.10	0.05
Positive self	0.13	0.05	0.15	0.07	0.13	0.06	0.15	0.06	0.14	0.06
Positive not-self	0.12	0.06	0.09	0.07	0.11	0.11	0.12	0.08	0.11	0.08
EXPERIMENT 2										
Negative self	0.09	0.10	0.06	0.06	0.07	0.09	0.09	0.06	0.08	0.08
Negative not-self	0.04	0.03	0.03	0.03	0.04	0.02	0.04	0.03	0.04	0.03
Positive self	0.10	0.05	0.06	0.04	0.08	0.04	0.09	0.07	0.08	0.05
Positive not-self	0.05	0.05	0.04	0.05	0.04	0.06	0.06	0.07	0.05	0.06
EXPERIMENT 3										
Negative self	0.08	0.09	0.10	0.06	0.10	0.10	0.06	0.07	0.08	0.08
Negative not-self	0.07	0.04	0.06	0.04	0.05	0.04	0.06	0.03	0.06	0.04
Positive self	0.09	0.05	0.08	0.05	0.09	0.05	0.08	0.05	0.08	0.05
Positive not-self	0.06	0.06	0.08	0.09	0.04	0.06	0.04	0.06	0.06	0.07

Self: self-descriptive; Not-self: not-self-descriptive. LA, low-anxious; HA, high-anxious; REP, repressor; DHA, defensive high-anxious.

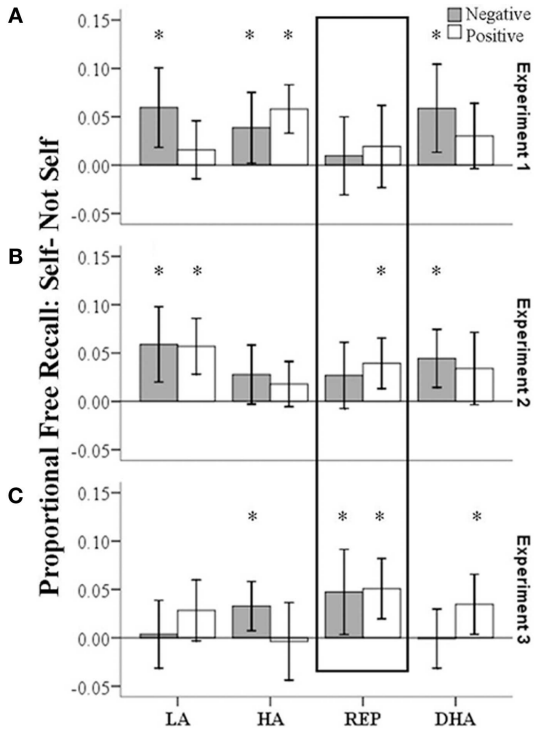


FIGURE 1 | Differences in recall proportions of words previously judged as self-descriptive minus words judged as not-self-descriptive. **(A)**: experiment 1, **(B)**: experiment 2, **(C)**: experiment 3. LA, low-anxious; HA, high-anxious; REP, repressor; DHA, defensive high-anxious. Asterisks indicate significantly better recall of self-descriptive compared to not self-descriptive words.

the free-recall advantages due to self-descriptiveness and valence in each group in experiment 1). We found that within the positive words, only HA individuals had a recall advantage of positive self-descriptive compared to positive not-self-descriptive words [$t(25) = 4.85$, $p < 0.01$, $d = 1.94$]. However, we observed better recall of negative self-descriptive than negative not-self-descriptive words in all groups except the REP group, differences with moderate to large effect sizes [LA: $t(21) = 3.00$, $p < 0.01$, $d = 1.31$; HA: $t(25) = 2.14$, $p < 0.05$, $d = 0.86$; DHA: $t(18) = 2.66$, $p < 0.05$, $d = 1.25$]. The REP group was the only group without a significant free-recall advantage for negative self-descriptive words over negative not-self-descriptive words in immediate recall [$t(27) = 0.54$, $p > 0.1$, $d = 0.21$]. This result conceptually replicates Fujiwara et al. (2008).

Would this differential recall pattern become more pronounced with a delay? To answer this question and address hypothesis 2, free-recall data from experiment 2 (delayed recall) was analyzed in the same way (see **Table 3**; **Figure 1B**). Similar as in experiment 1, we observed a main effect of self-judgment [$F(1, 101) = 21.23$, $p < 0.001$, $\eta_{partial}^2 = 0.17$], controlling for the covariate "presence/absence of other participants during the experiment." The main effect indicated better recall of words that were previously judged as self-descriptive compared to words that were judged as not-self-descriptive. Furthermore, we found an interaction between anxiety and defensiveness [$F(1, 101) = 8.35$, $p < 0.01$, $\eta_{partial}^2 = 0.08$]. A one-way ANOVA comparing groups on overall recall proportions [$F(1, 102) = 7.85$, $p < 0.05$] and *post hoc* Scheffé tests indicated that LA participants had better overall free-recall than HA participants (LA: mean $= 0.07 \pm 0.03$; HA: mean $= 0.05 \pm 0.02$). No further main effects or interactions were observed. Specifically, there was no significant four-way interaction [$F(1, 101) = 0.12$, $p > 0.1$, $\eta_{partial}^2 = 0.001$], contrary to experiment 1. Of note, there were differences in experiments 1 and 2: we had detected anxiety main effects in both of judgment ratios only in experiment 2, pointing to possible anxiety-based differences in numbers of negative and positive items judged as self-descriptive or not-self-descriptive in experiment 2. Thus, a repeated-measures ANCOVA on free-recall proportions in experiment 2 was conducted including both judgment ratios as covariates. The results of this ANCOVA were similar: controlling for the judgment ratios, the four-way interaction was still not significant [$F(1, 99) = 0.27$, $p > 0.1$, $\eta_{partial}^2 = 0.003$]. Thus, counter to our second hypothesis, REP had no reduced recall of negative self-descriptive information after the delay compared to any of the other groups and we did not observe an exaggeration of the within-group difference we had observed in experiment 1.

Experiment 3 (delayed recall with priming), which was intended to prime potential recall failures for unfavorable information in REP, is presented next (cf. **Table 3**; **Figure 1C**). Controlling for the covariate "presence/absence of other participants during the experiment," we observed a main effect of self-judgment [$F(1, 94) = 12.08$, $p < 0.001$, $\eta_{partial}^2 = 0.11$], indicating better recall of words that were previously judged as self-descriptive than words that were judged as not-self-descriptive. Although this effect was similar to that observed in experiments 1 and 2, the effect size was smaller. The main effect was qualified by a four-way interaction between valence, self-judgment, anxiety, and defensiveness [$F(1, 94) = 4.97$, $p < 0.05$, $\eta_{partial}^2 = 0.05$]. Following up on this interaction, there were no between-group differences in any of the four recall proportions [negative self-descriptive: $F(3, 95) = 1.23$, $p > 0.1$; negative not-self-descriptive: $F(3, 95) = 1.39$, $p > 0.1$; positive self-descriptive: $F(3, 95) = 0.54$, $p > 0.1$; positive not-self-descriptive: $F(3, 95) = 1.89$, $p > 0.1$]. Secondly, we conducted the mixed repeated-measures ANOVA within each of the four groups separately. The main effect of self-judgment was only present in REP [$F(1, 22) = 11.36$, $p < 0.01$, $\eta_{partial}^2 = 0.34$], but not in LA [$F(1, 26) = 1.32$, $p > 0.1$, $\eta_{partial}^2 = 0.04$], HA [$F(1, 27) = 1.53$, $p > 0.1$, $\eta_{partial}^2 = 0.05$], or DHA [$F(1, 20) = 2.75$, $p > 0.1$, $\eta_{partial}^2 = 0.12$]. Finally, within-group paired t-tests showed that REP participants were the only group with a significant recall advantage for self-descriptive over not-self-descriptive words, for both negative words [$t(22) = 2.23$, $p < 0.05$, $d = 0.95$] and positive words [$t(22) = 3.38$, $p < 0.01$, $d = 1.44$; see also **Figure 1C**], and both these differences had large effect sizes. HA showed such self-descriptiveness advantage in recall only for negative words [$t(27) = 2.63$, $p < 0.05$, $d = 1.01$], but not positive words [$t(27) = -0.19$, $p > 0.5$, $d = -0.07$], DHA only for positive words [$t(20) = 2.33$, $p < 0.05$, $d = 1.04$], but not negative words [$t(20) = -0.06$, $p > 0.5$, $d = -0.004$]. The LA group showed neither significant self-descriptiveness advantage in recall [negative: $t(26) = 0.22$, $p > 0.5$, $d = 0.09$; positive:

$t(26) = 1.85$, $p < 0.1$, $d = 0.73$], although approaching significance for positive words. Thus, the priming task evoked the strongest self-descriptiveness advantage in subsequent recall in REP, regardless of word valence.

PRIMING

Word identification accuracy in the lexical decision task in experiment 3 was close to ceiling (proportions of 0.92 ± 0.05 of all items were correctly identified), did not differ between groups, and was therefore not analyzed further. Priming scores, subtracting response times to words from the encoding task from response times to new words, were analyzed, again as a function of valence (positive/negative), prior self-judgment (self-descriptive/not-self-descriptive), anxiety (high/low), and defensiveness (high/low). Controlling for the covariate "presence/absence of other participants during the experiment," we found main effects of valence [$F(1, 94) = 14.41$, $p < 0.001$, $\eta_{partial}^2 = 0.13$] and self-judgment [$F(1, 94) = 10.48$, $p < 0.01$, $\eta_{partial}^2 = 0.10$]. Participants showed more priming for negative words [mean = 25.07 ms (SE = 3.2 ms)] than for positive words [mean = 9.57 ms (SE = 3.74 ms)] and more priming for self-descriptive words [mean = 22.54 ms (SE = 3.41 ms)] than for not-self-descriptive words [mean = 12.1 ms (SE = 2.87 ms)]. No further main effects or interactions were observed. The four-way interaction involving valence, self, anxiety, and defensiveness was far from significant [$F(1, 94) = 0.4$, $p > 0.5$, $\eta_{partial}^2 = 0.004$]. Thus, anxiety, defensiveness or their interaction did not influence priming performance at the delay.

DISCUSSION

Repressors were the only group without a recall advantage for negative words they had previously judged as self-descriptive compared to words they had not endorsed as self-descriptive in experiment 1. This replicates our previous results (Fujiwara et al., 2008) in an independent sample, despite the fact that in the current setting we used three times as many words, a more gradual 4-point self-judgment scale and only a self-judgment task (but no valence-judgment task). The gradual 4-point scale was used to allow more nuanced self-descriptiveness judgments than simple yes/no answers. By having less extreme options available we intended to allow participants to be more realistic in their self-judgments and intended to test more graded self-descriptiveness effects on memory. While we had to combine the 4-point answers into two categories (self-descriptive and not-self-descriptive) to avoid excessive loss of data, this type of answering during the encoding task critically differs from the simple two options during encoding in Fujiwara et al. (2008) and could have altered participants' experience during encoding in the current experiment. This suggests that although the effect is small, it appears to be real. However, counter to our second hypothesis, this relatively lowered recall for negative self-descriptive information within the repressor group did not become more pronounced in free-recall after a 2-day delay in experiment 2. Note also that repressors consistently had the highest positivity-judgment ratio in each study, but only in study 1 did we see their relatively reduced recall.

We had good reasons to expect that self-descriptiveness may increase repressors' recall biases over a delay. Hock and Krohne (Hock and Krohne, 2004; Krohne and Hock, 2008; Peters et al., 2012) found that repressors recalled threat-related information less than non-repressor groups only after a delay. The definition of repressive coping style by Weinberger (1990; Weinberger et al., 1979) states that individuals with a repressive coping style are not just sensitive to any threat but particularly to threat directed at their positive self-view. Various findings (e.g., in thought suppression or directed forgetting paradigms; Myers et al., 1998; Barnier et al., 2004; Myers and Derakshan, 2004) also point to a particular vulnerability of repressors to self-related threat. Our own previous study (Fujiwara et al., 2008) also found no immediate recall reductions in repressors for negative information that had simply been judged with regard to valence, but recall reductions occurred if encountered in a self-relevant encoding task.

There are several possible explanations why we did not observe stronger self-serving memory biases over the delay in repressors. First, the "threat" imposed by our task can reasonably be conceived as mild although the results of experiment 1 imply that even this mild threat was sufficient to show differential retrieval patterns against negative self-descriptive information only in repressors. Saunders et al. (2012) found that repressors are more prone to self-serving recall distortions in mnemic neglect paradigms than non-repressors, especially those with high anxiety levels. An important difference in our procedure compared to mnemic neglect paradigms is that here participants self-selected information as self-descriptive or not-self-descriptive rather than being given hypothetical self-view threatening feedback by the experimenter. Thus, it is possible that in our study, a motivation to retrieve information that had previously been deemed self-diagnostic superseded any potential self-protective biases in memory, and perhaps even more so after the delay. Secondly, our 2-day delay was (for practical reasons) shorter by a day than that in Krohne and Hock's work. Thus, perhaps we did not detect self-serving recall biases in repressors after the 2-day delay simply due to a truncated wait time before such biases would emerge. However, we believe it is unlikely that this difference caused the difference in results. Repressors after 2 days started to show a self-descriptiveness advantage in free-recall, especially for positive words but also (non-significantly so) for negative words. It is difficult to imagine how repressors would first show a self-serving bias in immediate recall, which became eliminated after a 2-day delay, and which would then be reinstated or even exaggerated after 3 days.

Fading affect bias, a phenomenon describing faster decay of information associated with negative emotional experiences compared to positive emotions over time (Walker and Skowronski, 2009) may also have contributed to our results. After 2 days, any potential threat experienced by repressors immediately post-judgment, leading to immediate relative recall reductions for negative self-descriptive words, may have dissipated. To our knowledge, the effects of a test delay on the self-descriptiveness effect as tested in experiment 2 and 3 have not been reported previously. However, self-reference effects in memory (superior memory for information evaluated with reference to oneself, compared to information evaluated with reference to someone else) tend to become stronger over time (Symons and Johnson, 1997). Differences in self-judgments (self-descriptive/not-self-descriptive) explained 10% of the variance in free-recall at immediate test in experiment 1. They explained 17% at the delayed test in experiment 2, pointing to an increase of the self-descriptiveness effect in

memory over a delay. Thus, self-descriptiveness effects, regardless of valence, may have counteracted any potential increase in self-serving memory biases in repressors over time. Results of experiment 3 can be interpreted in favor of this explanation as well. While cueing diminished self-descriptiveness effects in free-recall in all non-repressor groups, mainly due to increasing recall of not-self-descriptive information, repressors were the only group retaining the self-descriptiveness effect after cueing. Perhaps, repressors more so than any of the other groups, had been reminded of information they had previously endorsed as pertaining to themselves. They could have then used this information to produce the most self-consistent recall pattern rather than a positively biased one.

In this context, the assessment of coping styles using the BIDR-SDE subscale in our studies may have played a critical role. The BIDR-SDE subscale measures private, overconfident, egoistic self-deception (Paulhus, 1991; Paulhus and John, 1998) rather than outward-directed conformism to social norms as assessed with the Marlowe–Crowne Social Desirability Scale (MCSDS; Crowne and Marlowe, 1964), which is more commonly used in the repressive coping style literature following Weinberger et al. (1979). Repressors need to convince themselves and not just others of their own invulnerability against anxiety (Weinberger et al., 1979; Weinberger, 1990). Thus, the SDE part of the BIDR seemed better suited to assess the repressive coping style than the MCSDS (see also Weinberger and Davidson, 1994; Ashley and Holtgraves, 2003). However, individuals with high BIDR-SDE scores are also characterized by mental rigidity. For example, they perseverate in performing erroneous behavior in the face of failure (Peterson et al., 2003). It appears possible then that our high BIDR-SDE repressors may have reinterpreted initially self-devaluing information in a more positive light over the delay and therefore might have been well able to retrieve it, especially so when cued with an innocuous priming task. Therefore, despite the normative ratings used to select the words in this study (Anderson, 1968), it is possible that some of the negative (unlikable) words indeed represented desirable characteristics to repressors, particularly after some deliberation during the delay.

This interpretation does not run counter to Hock and Krohne's findings (Hock and Krohne, 2004; Krohne and Hock, 2008; Peters et al., 2012). Rather it suggests that when assessing coping styles in different ways, memories for valenced materials and self-related materials decay differently over time depending on how repressive coping style is measured and whether self-involvement is present. Avoidance of (anxiety-induced) arousal underlies repressive coping in the MCI. Hence, arousal-inducing information may not be consolidated to the same extent in (MCI-)repressors than in groups of non-repressors, which could result in decreased memory for such information over time. Conversely, when using the BIDR-SDE to assess the defensiveness dimension of Weinberger's conceptualization of repressive coping, information inconsistent with an over-positive self-view may become reinterpreted over time and seems to remain accessible.

Future extensions of the current studies would need to incorporate both valence- and self-descriptiveness judgments to test our suggestions. As such, one should assess whether repressors indeed judge originally self-descriptive negative information in a more positive way following a delay. Furthermore, the experiments involved either individual or group testing settings. Even though this seemed to have only minor influences on the results, it would be optimal to keep the testing environment more consistent in future studies, e.g., by only testing participants individually. An important limitation in this field in general is the relatively arbitrary separation of coping style groups. This can be remedied by using substantially larger samples and a continuous measure of repressive coping (as suggested by Mendolia, 2002). Another way to select repressive individuals might be to assess physiological reactivity (e.g., after a stress induction task) in conjunction with self-report, as done in some previous studies (e.g., Coifman et al., 2007). Repressors selected this way would show normal to high physiological reactivity in conjunction with an under-reporting of the stress experience, which is at the core of Weinberger's characterization of the repressive coping style.

CONCLUSION

In this set of studies, individuals with a repressive coping style showed selectively lowered immediate recall of negative self-descriptive information, but not after a 2-day delay. This result may seem to run counter to suggestions of repressors having an exaggerated bias against retrieving negative memories after a delay. However, we suggest that repressors, at least when assessed according to Weinberger's classification scheme, may reinterpret initially negative self-relevant information in a more positive light after a delay, and therefore no longer experience the need to bias their recall at a delay.

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REFERENCES

Anderson, M. C., and Green, C. (2001). Suppressing unwanted memories by executive control. *Nature* 410, 366–369. doi:10.1038/35066572

Anderson, N. H. (1968). Likableness ratings of 555 personality-trait words. *J. Pers. Soc. Psychol.* 9, 272–279. doi:10.1037/h0025907

Ashley, A., and Holtgraves, T. (2003). Repressors and memory: effects of self-deception, impression management, and mood. *J. Res. Pers.* 37, 284–296. doi:10.1016/S0092-6566(02)00567-6

Avero, P., Corace, K. M., Endler, N. S., and Calvo, M. G. (2003). Coping styles and threat processing. *Pers. Individ. Dif.* 35, 843–861. doi:10.1016/S0191-8869(02)00287-8

Barnier, A., Levin, K., and Maher, A. (2004). Suppressing thoughts of past events: are repressive copers good suppressors? *Cogn. Emot.* 18, 513–531. doi:10.1080/02699930341000428

Broomfield, N. M., and Turpin, G. (2005). Covert and overt attention in trait anxiety: a cognitive psychophysiological analysis. *Biol. Psychol.* 68, 179–200. doi:10.1016/j.biopsycho.2004.04.008

Brosschot, J. F., De Ruiter, C., and Kindt, M. (1997). Recall and recognition of threatening, pleasant, and neutral words in repressors. *Eur. J. Pers.* 13, 1–14. doi:10.1002/(SICI)1099-0984(199901/02)13:1<1::AID-PER313>3.3.CO;2-4

Caldwell, T. L., and Newman, L. S. (2005). The timeline of threat processing in repressors: more evidence for early vigilance and late avoidance. *Pers. Individ. Dif.* 38, 1957–1967. doi:10.1016/j.paid.2004.12.004

Calvo, M. G., and Eysenck, M. W. (2000). Early vigilance and late avoidance of threat processing: repressive coping versus high/low anxiety. *Cogn. Emot.* 14, 763–787. doi:10.1080/02699930050156627

Coifman, K. G., Bonanno, G. A., Ray, R. D., and Gross, J. J. (2007). Does repressive coping promote resilience? Affective-autonomic response discrepancy during bereavement. *J. Pers. Soc. Psychol.* 92, 745–758. doi:10.1037/0022-3514.92.4.745

Crowne, D. P., and Marlowe, D. (1964). *The Approval Motive*. New York: John Wiley & Sons.

Davis, P. J. (1990). "Repression and the inaccessibility of emotional memory," in *Repression and Dissociation*, ed. J. L. Singer (Chicago: Chicago University Press), 387–434.

Davis, P. J., and Schwartz, G. E. (1987). Repression and the inaccessibility of affective memories. *J. Pers. Soc. Psychol.* 52, 155–162. doi:10.1037/0022-3514.52.1.155

Derakshan, N., Eysenck, M. W., and Myers, L. B. (2007). Emotional information processing in repressors: the vigilance-avoidance theory. *Cogn. Emot.* 21, 1585–1614. doi:10.1080/02699930701499857

Dickson, J. M., Moberly, N. J., Hannon, E. M., and Bates, G. W. (2009). Are repressors so special after all? Specificity of negative personal events as a function of anxiety and defensiveness. *J. Res. Pers.* 43, 386–391. doi:10.1016/j.jrp.2009.01.002

Erdelyi, M. H. (2006). The unified theory of repression. *Behav. Brain Sci.* 29, 499–511. doi:10.1017/S0140525X06009113

Freud, S. (1957/1915). "Repression," in *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, ed. J. Strachey (London: Hogarth Press), 141–158.

Fujiwara, E., Levine, B., and Anderson, A. K. (2008). Intact implicit and reduced explicit memory for negative self-related information in repressive coping. *Cogn. Affect. Behav. Neurosci.* 8, 254–263. doi:10.3758/CABN.8.3.254

Geraerts, E., Dritschel, B., Kreplin, U., Miyagawa, L., and Waddington, J. (2012). Reduced specificity of negative autobiographical memories in repressive coping. *J. Behav. Ther. Exp. Psychiatry* 43(Suppl. 1), S32–S36. doi:10.1016/j.jbtep.2011.05.007

Geraerts, E., Merckelbach, H., Jelicic, M., and Habets, P. (2007). Suppression of intrusive thoughts and working memory capacity in repressive coping. *Am. J. Psychol.* 120, 205–218.

Geraerts, E., Merckelbach, H., Jelicic, M., and Smeets, E. (2006). Long term consequences of suppression of intrusive anxious thoughts and repressive coping. *Behav. Res. Ther.* 44, 1451–1460. doi:10.1016/j.brat.2005.11.001

Graesser, A. C., and Bower, G. H. (1990). *The Psychology of Learning and Motivation: Advances in Research and Theory*. New York: Academic Press.

Green, J. D., and Sedikides, C. (2004). Retrieval selectivity in the processing of self-referent information: testing the boundaries of self-protection. *Self Identity* 3, 69–80. doi:10.1080/13576500342000059

Green, J. D., Sedikides, C., and Gregg, A. P. (2008). Forgotten but not gone: the recall and recognition of self-threatening memories. *J. Exp. Soc. Psychol.* 44, 547–561. doi:10.1016/j.jesp.2007.10.006

Hertel, P., and McDaniel, L. (2010). The suppressive power of positive thinking: aiding suppression-induced forgetting in repressive coping. *Cogn. Emot.* 7, 1239–1249. doi:10.1080/02699930903172377

Hock, M., and Krohne, H. W. (2004). Coping with threat and memory for ambiguous information: testing the repressive discontinuity hypothesis. *Emotion* 4, 65–86. doi:10.1037/1528-3542.4.1.65

Krohne, H. W., and Egloff, B. (1989). *Das Angstbewältigungsinventar (ABI)*. Frankfurt: Swets Test Services.

Krohne, H. W., Egloff, B., Varner, L. J., Burns, L. R., Weidner, G., and Ellis, H. C. (2000). The assessment of dispositional vigilance and cognitive avoidance: factorial structure, psychometric properties, and validity of the Mainz Coping Inventory. *Cognit. Ther. Res.* 24, 297–311. doi:10.1023/A:1005511320194

Krohne, H. W., and Hock, M. (2008). Cognitive avoidance, positive affect, and gender as predictors of the processing of aversive information. *J. Res. Pers.* 42, 1572–1584. doi:10.1016/j.jrp.2008.07.015

Krohne, H. W., and Hock, M. (2011). Anxiety, coping strategies, and the processing of threatening information: investigations with cognitive-experimental paradigms. *Pers. Individ. Dif.* 50, 916–925. doi:10.1016/j.paid.2010.08.001

Mendolia, M. (2002). An index of self-regulation of emotion and the study of repression in social contexts that threaten or do not threaten self-concept. *Emotion* 2, 215–232. doi:10.1037/1528-3542.2.3.215

Mund, M., and Mitte, K. (2012). The costs of repression: a meta-analysis on the relation between repressive coping and somatic diseases. *Health Psychol.* 31, 640–649. doi:10.1037/a0026257

Myers, L. B., Brewin, C. R., and Power, M. J. (1998). Repressive coping and the directed forgetting of emotional material. *J. Abnorm. Psychol.* 107, 141–148. doi:10.1037/0021-843X.107.1.141

Myers, L. B., and Derakshan, N. (2004). To forget or not to forget: what do repressors forget and when do they forget? *Cogn. Emot.* 18, 495–511. doi:10.1080/02699930341000419

Oldenburg, C., Lundh, L.-G., and Kivisto, P. (2002). Explicit and implicit memory, trait anxiety, and repressive coping style. *Pers. Individ. Dif.* 32, 107–119. doi:10.1016/S0191-8869(01)00009-5

Paul, V. G., Rauch, A. V., Kugel, H., Ter Horst, L., Bauer, J., Dannlowski, U., et al. (2012). High responsivity to threat during the initial stage of perception in repression: a 3 T fMRI study. *Soc. Cogn. Affect. Neurosci.* 7, 980–990. doi:10.1093/scan/nsr080

Paulhus, D. L. (1991). "Measurement and control of response bias," in *Measures of Personality and Social Psychological Attitudes*, eds J. P. Robinson, P. R. Shaver, and L. S. Wrightsman (San Diego: Academic Press), 17–59.

Paulhus, D. L., and John, O. P. (1998). Egoistic and moralistic biases in self-perception: the interplay of self-deceptive styles with basic traits and motives. *J. Pers.* 66, 1025–1060. doi:10.1111/1467-6494.00041

Peters, J. H., Hock, M., and Krohne, H. W. (2012). Sensitive maintenance: a cognitive process underlying individual differences in memory for threatening information. *J. Pers. Soc. Psychol.* 102, 200–213. doi:10.1037/a0026080

Peterson, J. B., Deyoung, C. G., Driver-Linn, E., Séguin, J. R., Higgins, D. M., Arseneault, L., et al. (2003). Self-deception and failure to modulate responses despite accruing evidence of error. *J. Res. Pers.* 37, 205–223. doi:10.1016/S0092-6566(02)00569-X

Saunders, J., Worth, R., and Fernandes, M. (2012). Repressive coping style and mnemic neglect. *J. Exp. Psychopathol.* 3, 346–367.

Spielberger, C. D., Gorsuch, R. L., Lushene, R. E., Vagg, P. R., and Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Symons, C. S., and Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol. Bull.* 121, 371–394. doi:10.1037/0033-2909.121.3.371

Walker, W. R., and Skowronski, J. J. (2009). The fading affect bias: but what the hell is it for? *Appl. Cogn. Psychol.* 23, 1122–1136. doi:10.1002/acp.1614

Weinberger, D. A. (1990). "The construct validity of the repressive coping style," in *Repression and Dissociation*, ed. J. L. Singer (Chicago: Chicago University Press), 337–386.

Weinberger, D. A., and Davidson, M. N. (1994). Styles of inhibiting emotional expression: distinguishing repressive coping from impression management. *J. Pers.* 62, 587–613. doi:10.1111/j.1467-6494.1994.tb00310.x

Weinberger, D. A., Schwartz, G. E., and Davidson, R. J. (1979). Low-anxious, high-anxious, and repressive coping styles: psychometric patterns and behavioral and physiological responses to stress. *J. Abnorm. Psychol.* 88, 369–380. doi:10.1037/0021-843X.88.4.369

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Memory accessibility and medical decision-making for significant others: the role of socially shared retrieval-induced forgetting

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Medical decisions will often entail a broad search for relevant information. No sources alone may offer a complete picture, and many may be selective in their presentation. This selectivity may induce forgetting for previously learned material, thereby adversely affecting medical decision-making. In the study phase of two experiments, participants learned information about a fictitious disease and advantages and disadvantages of four treatment options. In the subsequent practice phase, they read a pamphlet selectively presenting either relevant (Experiment 1) or irrelevant (Experiment 2) advantages or disadvantages. A final cued recall followed and, in Experiment 2, a decision as to the best treatment for a patient. Not only did reading the pamphlet induce forgetting for related and unmentioned information, the induced forgetting adversely affected decision-making. The research provides a cautionary note about the risks of searching through selectively presented information when making a medical decision.

Keywords: memory accessibility, retrieval-induced forgetting, medical information

INTRODUCTION

Medical decisions, like many other kinds of decisions, will often entail a broad search for a wide range of relevant information. When deciding which treatment option to pursue, people might visit one or more doctor(s), scan the Internet, talk to friends and acquaintances, and acquire and carefully peruse relevant brochures and other printed material. Given the commercial and often biased nature of many sources of information, as well as time constraints faced by the investigator, the received information might highlight some facts, while limiting easy access to other, equally relevant ones (Simon, 1985; Gigerenzer and Goldstein, 1996). For instance, the Pfizer website for Lipitor (Lipitor Official Website, 2006) (http://www.lipitor.com) describes the drug's side effects and precautions only in a side bar or in a manner that demands that the viewer scrolls down to the bottom of the web page. We are interested here in how selective presentation of information affects the subsequent accessibility of the "unmentioned" items. Moreover, we want to explore whether any shift in accessibility potentially influences medical decisions.

In many instances, medical decisions are best characterized as based on memory for the "gist" of acquired information (Reyna and Lloyd, 2006). For instance, people often fail to remember the exact figures provided about the risk of a medical procedure, even though they may remember the "general" pattern (Reyna and Hamilton, 2001). Providing the gist about the relative risk of different treatment options can be more effective than providing precise information (for a review, see Reyna, 2008).

In some situations, however, access to precise information may be desirable for the medical decision-maker. When deciding what citrus fruit to have at breakfast, decision-makers may be at an advantage if they know precisely that navel and Valencia oranges are allowable if taking Lipitor, but not Cara Cara oranges or grapefruit. Knowing simply that some citrus fruits are allowable may not be sufficient. In such situations, knowing and accessing specific information might become critical for making effective judgments and decisions (see Lichtenstein et al., 1978; Lynch and Srull, 1982; Feldman and Lynch, 1988; Johnson et al., 2007; see also Tversky and Kahneman, 1973; Menon and Raghubir, 2003).

The present study, then, addresses two issues: how does selective exposure to relevant medical information affect mnemonic accessibility? And in instances in which precise information is needed, does any shift in mnemonic accessibility influence medical decision-making? We focus on situations in which the decision-maker is first exposed to information on the treatments suitable for a disease and then re-exposed to a selective rendering of those treatments, as might be the case when a patient turns to the Internet to follow-up on the discussion they had with their doctor. With such re-exposures, even if time constraints do not prevent a complete and exhaustive search, there might nevertheless be selectivity, in that, as noted, all the relevant information encountered initially might not easily be found during an Internet search. Our interest is not in the practice effects one might expect to find with re-exposure, but in the forgetting that might occur when information goes unmentioned.

There are several reasons why forgetting might occur when previously known information goes unmentioned. First, the unmentioned information might decay if not rehearsed (Wixted, 2004). Second, and more critical for the present study, individuals might be *induced* to forget the unmentioned information if it is related to mentioned information. As the large literature on

retrieval-induced forgetting (RIF) suggests, when people selectively practice previously studied material, they are more likely to forget unpracticed memories related to the practiced material than unpracticed, unrelated memories (Anderson et al., 1994).

The standard RIF paradigm includes three experimental phases: a study phase, a selective practice phase, and a final recall phase. In the study phase participants study category-exemplars pairs such as: *fruit-apple*, *fruit-banana*, *clothes-dress*, *clothes-shirt*. A selective practice phase follows where participants are instructed to complete stems for half of the exemplars from half of the categories: *fruit-a____*, but not *fruit-banana*, nor any of the *clothes* items. This selective practice creates three types of items, depending on the retrieval status of each studied item: (1) items that were selectively practiced (Rp+: *fruit-apple*), (2) items that were unpracticed, but related to the practiced ones (Rp−: *fruit-banana*), and (3) items that were unpracticed and unrelated to those practiced (Nrp: *clothes-dress*; *clothes-shirt*). Finally, participants are asked to recall all exemplars from all categories presented in the study phase. The recall proportion measured in the final recall phase reveals both a practice effect for practiced items (that is, the recall proportion of Rp+ items larger than the recall proportion of Nrp items), but, more importantly for this paper, RIF is observed for the unpracticed, related material (that is, the recall proportion of Rp− items smaller than the recall proportion of Nrp items). If RIF were merely a matter of decay, the unpracticed memories related to the retrieved materials should be forgotten at the same rate as unpracticed memories unrelated to the retrieved material. In order to account for the observed RIF pattern, many researchers have argued that the retrieval of a desired memory will produce response competition from related memories, which must be inhibited if retrieval of the desired memory is to be successful (for a review, see Anderson and Levy, 2007; Storm and Levy, 2012). This inhibition lingers, producing the pattern of forgetting associated with RIF (for an alternative account, see Dodd et al., 2006).

Retrieval-induced forgetting is relevant to our present concerns because it can occur not only when probed individuals themselves selectively and overtly remember (within-individual RIF, or WI-RIF), but also when probed individuals attend to others remembering (socially shared RIF, SS-RIF; Cuc et al., 2007; Coman et al., 2009; Stone et al., 2010; Coman and Hirst, 2012; Hirst and Echterhoff, 2012). Hirst and his colleagues claim that SS-RIF occurs because attendees concurrently retrieve with the rememberer, and, as a result, find themselves also selectively remembering. In some instances of SS-RIF, the source of the memory can be physically present, as when a listener monitors the speaker for accuracy in a conversation. In other instances, it can be implied, as when someone reads written material. For reading, the source of the memory is the "author" of the material. SS-RIF differs from WI-RIF because in the latter case, the experimenter instructs participants to retrieve particular memories. Speakers or authors, when discussing the past, are, by definition, retrieving memories. Their listeners or readers, however, are not obligated to retrieve a memory along with the speaker or author. If they retrieve overtly, they are no longer a listener, but a speaker. If they retrieve covertly along with the speaker, it is entirely a choice that they alone have made. What is perhaps surprising is that listeners and readers appear to make the effort to concurrently, covertly retrieve in many instances, thereby manifesting SS-RIF.

Studies of SS-RIF, especially those involving written material, would suggest that selective practice[1] of medical information might induce forgetting for unpracticed, but related information. The result would be a hierarchy of accessibility, with the practiced information most accessible, the unpracticed, and unrelated to the practiced information moderately accessible, and the unpracticed information related to the practiced information least accessible. Our claim is that these differences in accessibility have consequences for the final medical decision. For instance, a person with back pain may initially learn about the advantages and disadvantages of two treatments, steroids and acupuncture, but may encounter only the advantages of the steroid treatment as they continue their search. They may also fail to encounter any information about acupuncture, given, perhaps, its "alternative-medicine" status. If SS-RIF is at work, they should in the end have more difficulty remembering the disadvantages of steroid treatment than the disadvantages of acupuncture. This difference in accessibility could affect their decision about which treatment to pursue.

The relation between RIF and decision-making has proven difficult to establish. Storm et al. (2005), for instance, found that RIF for positive and negative attributes of target individuals did not affect participants' impressions of the targets, at least as measured by likeability ratings. On the other hand, Iglesias-Parro and Gomez-Ariza (2006) found that the selective practice of previously studied material about job candidates influenced participants' employment judgments, but only in certain circumstances.

In the present study, we examined for the first time the relation between SS-RIF and medical decision-making. In Experiment 1, we determined whether we could find SS-RIF for medical information. As we noted, when reading, simultaneous retrieval of relevant memories is optional. SS-RIF will only occur if covert concurrent retrieval occurs (Cuc et al., 2007). We therefore wanted to determine, before proceeding to our questions about RIF and decision-making, whether selectively presented medically relevant material induced forgetting in previously learned medical information. Participants first learned about a fictitious disease, Wheeler's syndrome, including the advantages and disadvantages of treatment options. We chose to use as our stimulus material a fictitious disease because we wanted to avoid any effect prior knowledge might have had on memory. Other researchers have employed a similar strategy for similar reasons (e.g., John and Fischhoff, 2010). We sought to make the disease as realistic as possible by modeling it on known diseases. Participants then read a brochure that presented information selectively. The pamphlet discussed some treatments, while ignoring others, and stressed either advantages or disadvantages for these discussed treatments. A final recall test followed. The results of Experiment 1 should establish that the act of reading selectively presented information can induce forgetting in

[1]Selective practice in this context refers to selectively searching through different sources of medical information. In this search we are re-exposed to parts of previously learned information, while other parts either related or unrelated to the re-exposed one remain unmentioned.

initially encoded memories that are related to the practiced information.

Experiment 2 explored the more critical issue of whether the SS-RIF observed in Experiment 1 will influence decision-making. In order to understand this dynamic, we added a final decision-making task at the end of the experiment. Importantly, for Experiment 2 we changed the design of the material so as to exclude the possibility that retrieval practice effects might account for the final decision, thereby limiting any possible mnemonic effects to SS-RIF.

In both experiments, participants are asked to imagine that they are helping a friend make a decision. We could have asked participants to imagine that they had the described disease, but we reasoned that it might seem more realistic to participants to imagine that they were helping a friend with the described disease make a decision. People often experience medical decisions as stressful (Loewenstein, 2005; Luce, 2005) and, thus, besides receiving a doctor's opinion, they might consult with family and friends and rely on them for gathering treatment relevant information (Srirangam et al., 2003; Boehmer and Babayan, 2005).

EXPERIMENT 1

METHOD

Participants

Twenty-four undergraduate New School students received research credits for experimental participation. Data from two participants was discarded because in the debriefing phase of the study, they reported skepticism about the existence of the disease.

Materials

We constructed a 180-word description of Wheeler's syndrome. We made the information included in the description as plausible as possible by keeping close to syndrome descriptions in The Merck Manual, a widely used manual for diagnosis and treatments of medical disorders (Beers et al., 2006). Its definition, its prevalence and incidence were presented on one PowerPoint slide and its stages on another slide. On the third slide, participants learned information about Laura, whom participants were instructed to view as their fictional best friend. Four treatment options were then presented, in a random order, in a series of PowerPoint slides, one option per slide. On each slide, there was the name of the treatment, in bold type (e.g., **Propionic**, **Metabotropic**, etc.) and immediately below three advantages and three disadvantages, although they were not labeled as such. In fact, their benefits or costs were specific to the fictional friend the participants had learned about. For instance, the assertion that one treatment could be taken along with antacid medication was viewed as an advantage because Laura took antacid medication. The advantages were always framed "positively," e.g., "The treatment can be taken by people with stomach problems." (Laura has stomach problems.) Disadvantages were framed "negatively," as in "The treatment causes side effects for people with kidney problems." (Laura has kidney problems.) The form of the statement (whether it was an advantage, and thus positively framed or a disadvantage, and thus negatively framed) will be treated as a Valence factor in this experiment. Three evaluators analyzed each item of information included in each of the four treatments on the following dimensions: (a) salience of the items (e.g., whether some items were more salient and more likely to be easily remembered compared to others), and (b) relevance of items for Laura's case (e.g., whether some items were more relevant to her medical profile compared to others). Items evaluated as more salient and/or more connected to Laura's medical profile were discarded and replaced by new items. This pilot work indicated that participants should find each treatment – with its respective advantages and disadvantages – equally memorable and relevant for Laura's case. The advantages always preceded the disadvantages, but were otherwise randomly presented on the slide.

We chose to present advantages first for two related reasons. First, we wanted to avoid possible framing effects. Specifically, people tend to be more receptive at selecting treatment options when they are presented in a positive frame (Moxey et al., 2003). If we had varied the order, we might have built in biases that would have been difficult to compensate for, even with appropriate counterbalancing. Second, our decision reflects what we believe is the decision of many authors of medical brochures and Internet sites. A survey of medical websites indicated that most begin a description of a treatment with advantages, leaving the disadvantages to last. Indeed, it would seem odd to most people to begin a description of a treatment by articulating its disadvantages.

"Additional practice" was given with a brochure about Wheeler's syndrome. It contained a title page, which announced the disease's name and the sponsoring institution. The second page contained the same description of the disease presented during the original study phase. The third, and last, page described the treatment options, but selectively and in a random order. The top of the third page contained instructions asking the reader to indicate in the brochure whether each item under the treatment labels below would best be viewed as an advantage or a disadvantage. The treatments then followed. Two of the four initially presented treatment alternatives were presented, and for both of these treatments, either only the advantages or only the disadvantages were discussed. Participants were asked to indicate for each of the six statements whether they could be viewed as either an advantage or a disadvantage. These subjective judgments conformed to our classification 99% of the time. Which of the treatments were practiced was counterbalanced. To this end, we created four brochures.

This selective presentation of treatments with advantages or disadvantages allowed us to create Rp+, Rp−, and Nrp items. (The advantages or disadvantages presented in the brochure were Rp+; the non-mentioned advantages or disadvantages that were part of the same treatments with those mentioned were Rp−; and the advantages and disadvantages of the unmentioned treatments, Nrp.) *Valence* will refer to whether the Rp+ items were advantages (Positive Valence) or disadvantages (Negative Valence). Thus, page 3 contained two treatment options, with a total of either six advantages or six disadvantages. If Rp+ items were advantages, the Rp− items were disadvantages, and vice versa.

As to the description of Laura, it consisted of a 391-word profile. The inclusion of a target individual allowed the participant to understand the advantages and disadvantages as they apply to Laura. The profile indicated that Laura was recently diagnosed

with stage II Wheeler's Syndrome and included age, personal information, as well as medical history.

Design and procedure

All material was presented on an iMac computer. Participants first read the PowerPoint slides describing Wheeler's syndrome, each presented for 80 s. Then, Laura's profile appeared on the computer screen for 100 s. The screen then turned blank and participants were given 15 four-item forced choice recognition probes to test whether they remembered the information about Laura. The experimenter corrected any errors in the recognition test in front of the participants. The presentation of the four treatment alternatives commenced. Each treatment slide appeared on the computer screen for 45 s. Participants were then asked to peruse the brochure, which constituted the selective practice phase. They were given 7 min to do so. Finally, participants completed a cued recall for the advantages and disadvantages of the four treatments, with the name of the treatment serving as cue. There were 5 min of distraction between each phases of the experiment (see **Figure 1** for a summary of experimental phases for Experiment 1).

RESULTS AND DISCUSSION

To examine the effect of reading the brochure on memory accessibility, we first undertook two repeated measures analyses of variance (ANOVA), one for the practice effect (Rp+ > Nrp) and another for the induced forgetting effect (Nrp > Rp−). For the practice effect, when the advantages were mentioned in the brochure, we compared the proportion of the remembered Rp+ items out of the total number of Rp+ items with the proportion of remembered advantages of the Nrp treatments out of the total number of advantages of Nrp treatments (thereby comparing advantage with advantage in the final recall test). Similarly, for the induced forgetting effect, when the advantages were mentioned in the brochure we compared the proportion of the remembered Rp− items (related but unmentioned disadvantages) with the proportion of remembered disadvantages of the Nrp treatments (allowing us to compare disadvantages with disadvantages in the final recall). A similar comparison procedure was followed for both the practice and induced forgetting effects when disadvantages, instead of advantages, were practiced (see **Figure 2**).

For each ANOVA, there was one between-subject factor, Valence (whether advantages or disadvantages were practiced, we will use the terms *positive* and *negative*, respectively, to refer to the two) and one within-subject factor, Retrieval Type (Rp+ vs. Nrp or Rp− vs. Nrp). For the practice effect, we failed to find any significant main effects: Retrieval Type, $F(1, 18) = 2.26$, $p = 0.15$, $\eta_p^2 = 0.11$, and Valence, $F(1, 18) = 0.14$, $p = 0.72$, $\eta_p^2 = 0.00$. Nor did we find a significant interaction, $F(1, 18) = 0.02$, $p = 0.89$, $\eta_p^2 = 0.00$. As for the presence of SS-RIF, our main interest, we found a significant main effect for Retrieval Type, $F(1, 18) = 4.23$, $p < 0.05$, $\eta_p^2 = 0.19$, but not for Valence, $F(1, 18) = 0.34$, $p = 0.57$, $\eta_p^2 = 0.02$. The interaction was also not significant, $F(1, 18) = 2.45$, $p = 0.14$, $\eta_p^2 = 0.12$. We are not the first to find RIF in the absence of a practice effect (e.g., Storm et al., 2006). There is no *a priori* reason why the two must be connected in that they may involve different mechanisms. For instance, practice effects could involve the strengthening of a trace; RIF, the inhibition of a related trace. For SS-RIF, it is the retrieval of an item that triggers the processes that lead to induced forgetting, not the strengthening of the trace associated with the retrieved item (Anderson et al., 2000).

EXPERIMENT 2

Experiment 1 demonstrated that reading selectively presented medical material induced forgetting for unmentioned, but related information. Can this SS-RIF influence subsequent medical decisions? Of course, a practice effect could also affect decision-making by making the practiced items more accessible when the final decision is made. The experimental design of Experiment 1 does not allow us to disentangle easily practice and SS-RIF effects on a subsequent treatment decision. Inasmuch as our interest is the impact of SS-RIF on decision-making, in Experiment 2, we designed the material so that any contribution of a practice effect to the final treatment decision became irrelevant.

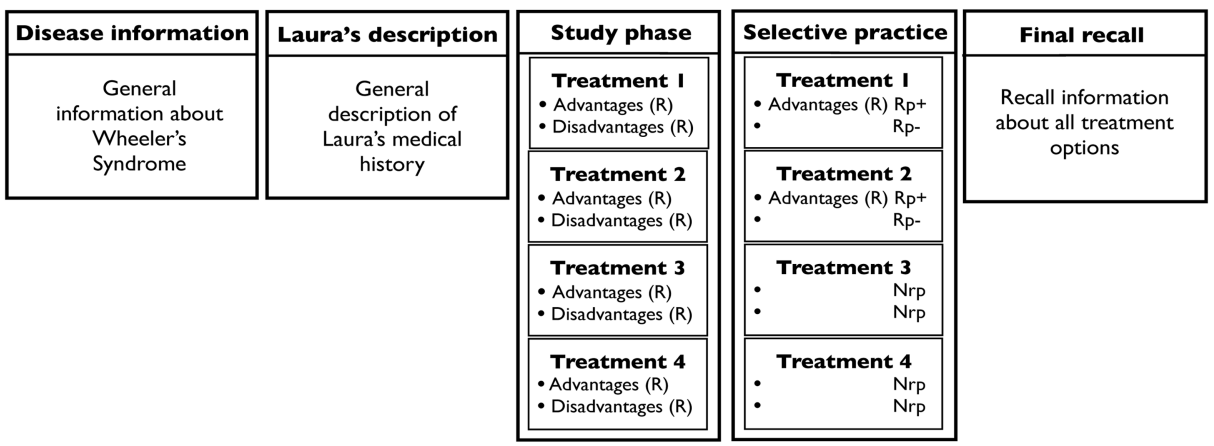


FIGURE 1 | Phases of Experiment 1, for the Positive Valence Condition. In the Study and Selective practice phases, R stands for relevant information; Rp+ for retrieval practice plus; Rp− for retrieval practice minus, and Nrp for no retrieval practice. In the Negative Valence condition, participants selectively practiced relevant disadvantages for two of the four treatments.

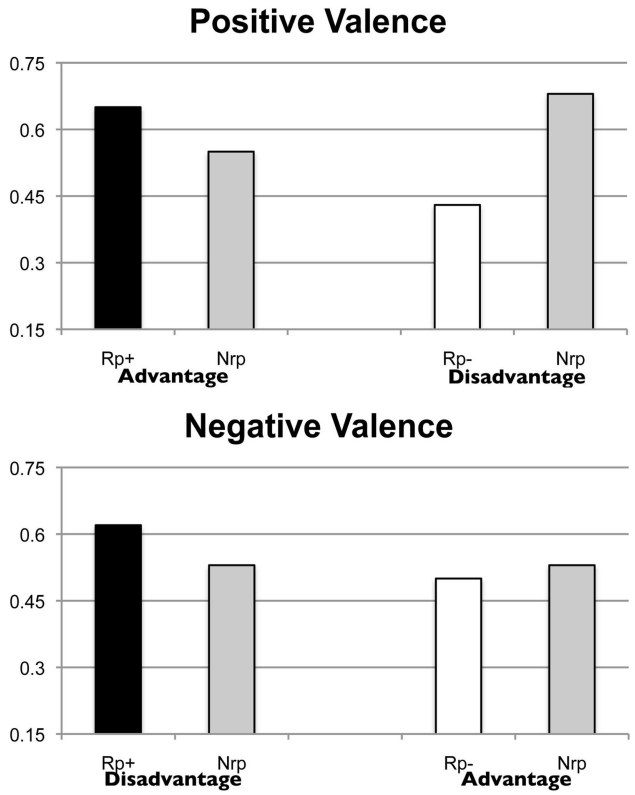


FIGURE 2 | Recall proportion for Rp+/Nrp and Rp−/Nrp items in Experiment 1, for the Positive Valence Condition (advantages received selective practice) (on the top), and the Negative Valence Condition (disadvantages received selective practice) (on the bottom). In the Positive Valence Condition, we compared Rp+ items (advantages) with Nrp advantage items, and Rp− items (disadvantages) with Nrp disadvantage items. Similarly, in the Negative Valence Condition, we compared Rp+ items (disadvantages) with Nrp disadvantage items, and Rp− items (advantages) with Nrp advantage items.

Specifically, the selective practice brochure was rewritten so that it only covered material irrelevant to Laura's case (e.g., "It can be taken by people who are allergic to aspirin," is irrelevant because Laura is not allergic to aspirin). The related, unmentioned information was, however, relevant (e.g., "It may have side effects for patients who have kidney problems," is relevant because Laura has kidney problems). We wanted to examine whether practicing irrelevant material could have the potential to decrease the accessibility of related, unmentioned information, which could, in turn, affect decision-making concerning Laura's treatment.

METHOD

Participants

Forty-eight graduate and undergraduate New School students participated in the experiment for class credit. Participants were divided evenly between the Test-Present and Test-Absent conditions and within these divisions, between the Positive and Negative Valence conditions.

Materials and design

The description of Wheeler's syndrome was the same as in Experiment 1. Similarly, each of the four treatments presented in the study phase included three advantages and three disadvantages, for a total of six items per treatment. Unlike Experiment 1, each advantage or disadvantage appeared on its own PowerPoint slide. Although in Experiment 1 all the advantages or disadvantages were relevant to Laura's case, in Experiment 2, a statement (be it an advantage or a disadvantage) could be relevant or irrelevant. We constructed four types of statements: *irrelevant advantage*, *irrelevant disadvantage*, *relevant advantage*, *and relevant disadvantage*. The statement "The treatment is recommended to people with Lupus" was *irrelevant* because Laura doesn't have Lupus and an *advantage* because it contains an inclusion criterion. A variant of the above statement – "The treatment is not recommended to people with Lupus," – was an *irrelevant disadvantage* because, although Laura doesn't have Lupus, the statement involves an exclusion criterion. On the other hand, the statement "The treatment can be taken by people with stomach problems" is both *relevant* (Laura has stomach problems) and an *advantage*, in that it contains an inclusion criterion. Finally, the statement "The treatment cannot be taken by people with stomach problems" is a *relevant disadvantage* because it contains an exclusion criterion. In what follows, we use the terms *positive* and *advantage*, as well as *negative* and *disadvantage*, interchangeably.

As for the brochure used in the practice phase, as in Experiment 1, only two treatments were included, with only the three irrelevant statements mentioned for each treatment. There were four brochures. Two of the brochures mentioned only the irrelevant advantages of the two treatments (constituting one set of brochures) and were given to participants in the Positive Valence Condition. The other two mentioned only the irrelevant disadvantages of the two treatments (constituting the second set) and were given to participants in the Negative Valence Condition. For each of the sets of the two brochures, which treatments were mentioned was counterbalanced, so that in one brochure Treatments 1 and 2 were mentioned, while Treatments 3 and 4 went unmentioned. For the other brochure in a set, Treatments 3 and 4 were mentioned, while Treatments 1 and 2 went unmentioned. Participants did not know that the mentioned information was irrelevant, inasmuch as, in Experiment 2, Laura's profile was presented toward the end of the experiment, in the decision-making phase, and the information is relevant or irrelevant only in the context of Laura's profile. The brochure had the same format as the brochure used in Experiment 1. Just as in Experiment 1, participants were asked to indicate for each of the six statements in the brochure whether they can be viewed as an advantage or a disadvantage. These subjective judgments conformed to our classification 94% of the time.

As to Laura's profile, it was similar to what was used in Experiment 1, with only slight stylistic changes. Unlike in Experiment 1, the profile was presented at the end of the experiment, when participants had to make a treatment decision, because we wanted to ensure that participants carefully read the material during the practice phase, which they might not have if they deemed it

irrelevant. People will often search for information on a disease of a friend before they know the details of her medical history.

Design and procedure

Participants first read the PowerPoint presentation about Wheeler's syndrome. They then read a presentation of the four treatment alternatives. Each item from each treatment was presented on a separate slide. For counterbalancing, half of the participants were exposed to four treatments containing three irrelevant advantages and three relevant disadvantages. In a mirror image pattern, the other half of the participants was presented with four treatments containing three irrelevant disadvantages and three relevant advantages.

After a distracter task, participants were given the brochure and asked to read it carefully. Half of the participants were given the two types of brochures designed for the Positive Valence Condition; the other half, the brochures designed for the Negative Valence Condition. Participants were given 7 min to read the brochure. As in Experiment 1, after another distracter task, in the Test-Present condition, participants completed a final recall test. They were given 10 min to complete it. The Test-Absent condition dropped the final recall test and extended the distracter task by 10 min. This control eliminated any potential effect that the final recall might have on decision-making. After the recall test or the extended distracter, participants received a hard copy of Laura's profile and were asked to choose the best treatment alternative for their friend's medical condition. They had as long as they wished to make a decision. See **Figure 3** for a summary of experimental phases of Experiment 2.

RESULTS AND DISCUSSION

As in Experiment 1, we first wanted to establish whether reading the brochure resulted in practice and SS-RIF effects. Here we examined the proportion of Rp+, Rp−, and Nrp items remembered in the final recall test of the Test-Present (experimental) condition. We then explored the relation between memory accessibility and decision-making.

Retrieval effects

We undertook two repeated measures ANOVA with Valence (whether irrelevant advantages or irrelevant disadvantages were practiced) as a between-subject factor, and Retrieval Type (Rp+ vs. Nrp or Rp− vs. Nrp) as a within-subject factor. Just as in Experiment 1, the recall proportion in the final recall test served as the dependent variable. As in Experiment 1, we compared the recall proportion of Rp advantages with the recall proportion of Nrp advantages, and similarly, we compared the recall proportion of Rp disadvantages with the recall proportion of Nrp disadvantages (see **Figure 4**). For the practice effect, we only found a significant main effect for Retrieval Type, $F(1, 22) = 22.87$, $p < 0.001$, $\eta_p^2 = 0.51$. There was no significant main effect for Valence, $F(1, 22) = 2.22$, $p = 0.15$, $\eta_p^2 = 0.09$, or for the interaction, $F(1, 22) = 0.71$, $p = 0.71$, $\eta_p^2 = 0.03$. That is, unlike Experiment 1, for which we did not find a practice effect, both advantages and disadvantages benefited from additional rehearsal here.

For the induced forgetting effect, we found significant main effects for both Retrieval Type, $F(1, 22) = 8.61$, $p < 0.01$, $\eta_p^2 = 0.18$, and Valence, $F(1, 22) = 4.45$, $p < 0.05$, $\eta_p^2 = 0.17$. There was no significant effect for the interaction between Retrieval Type and Valence, $F(1, 22) = 3.48$, $p = 0.08$, $\eta_p^2 = 0.13$. Importantly, we replicated Experiment 1 by finding SS-RIF.

One explanation for the observed induced forgetting effect is the output interference hypothesis, according to which impairment arises because the recalled Rp+ items interfere with the recall of Rp− items (Anderson and Spellman, 1995). As a test of this possibility, we followed Macrae and Roseveare (2002; see also Barnier et al., 2004) and ranked the Rp+ and Rp− items according to the order in which they appeared in each participant's final recall, with the lower ranking indicating an earlier recall. We then averaged the rankings for recalled Rp+ and Rp− items. We performed an ANOVA with Retrieval Type (Mean Rank Rp+ vs. Mean Rank Rp−) as a within-subject factor and Valence as a between-subject factor. We found neither significant main effects, nor a significant interaction (all

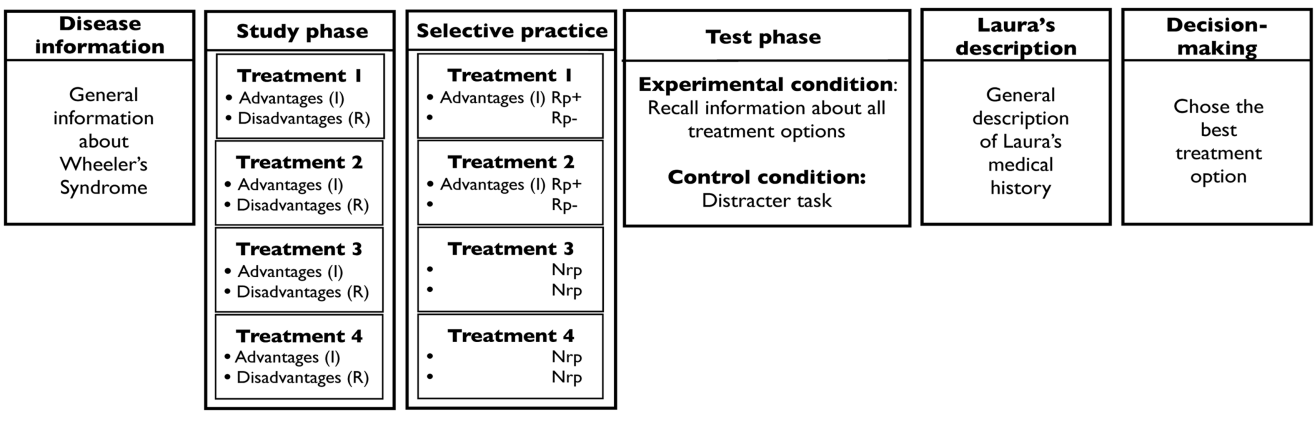


FIGURE 3 | Phases of Experiment 2, for the Positive Valence condition. In the Study and Selective practice phases, R stands for relevant information; I stands for irrelevant information; Rp+ for retrieval practice plus; Rp− for retrieval practice minus, and Nrp for no retrieval practice. In the Negative Valence condition, participants studied irrelevant disadvantages (the negatively stated version of irrelevant advantages) and relevant advantages (the positively stated version of relevant disadvantages) for each treatment, and selectively practiced irrelevant disadvantages for two of the four treatments.

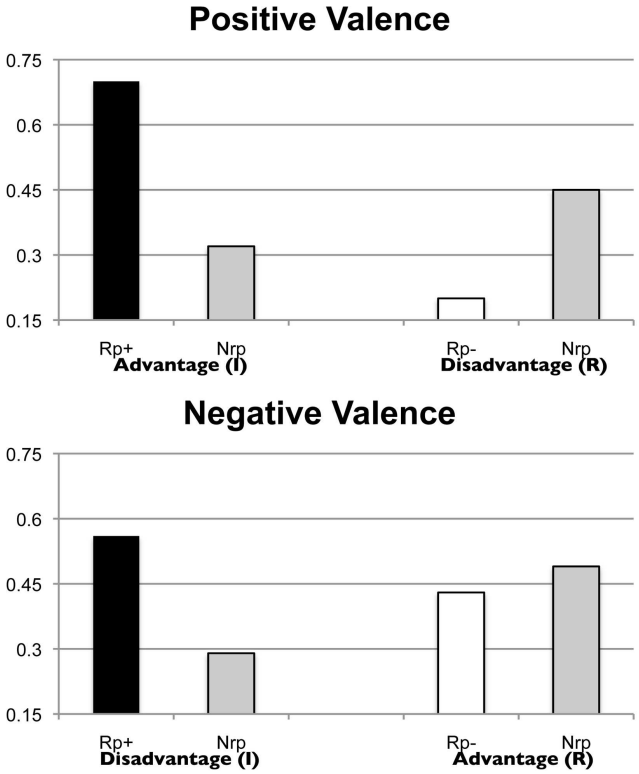


FIGURE 4 | Recall proportion for Rp+/Nrp and Rp−/Nrp items in Experiment 2, for the Positive Valence Condition (irrelevant advantages received selective practice) (on the top), and the Negative Valence Condition (irrelevant disadvantages received selective practice) (on the bottom). R stands for relevant, and I stands for irrelevant. In the Positive Valence Condition, we compared Rp+ items (irrelevant advantages) with Nrp advantage items, and Rp− items (irrelevant disadvantages) with Nrp disadvantage items. Similarly, in the Negative Valence Condition, we compared Rp+ items (irrelevant disadvantages) with Nrp disadvantage items, and Rp− items (irrelevant advantages) with Nrp advantage items.

p's > 0.20), which means that the induced forgetting effect is not due to the interference caused by the selective recall of Rp+ items.

Decision-making

As to the effect of SS-RIF on the decision about Laura's treatment, we undertook two separate analyses. In the first one, we classified the decisions as to whether they were consistent or inconsistent with what was assumed to be forgotten after reading the brochure. For example, if participants read a pamphlet about irrelevant advantages of some, but not all treatments, they would subsequently have difficulty accessing relevant, related and unmentioned disadvantages. As a result, according to the SS-RIF model, the disadvantages of those treatments discussed in the brochure should be less accessible than the disadvantages of the unrelated and unmentioned treatments. Inasmuch as the design of our stimulus material ensured that we can discount any influence practice might have on subsequent decision-making, then, in the present example, participants should prefer the mentioned treatments, in that their disadvantages are relatively inaccessible. Along similar lines, when irrelevant disadvantages are practiced, the relevant, related, and unmentioned advantages should subsequently be less accessible than the relevant advantages of the unrelated and unmentioned treatments. In such an instance, participants should prefer the treatments that were not discussed in the brochure because their advantages are more accessible. Inasmuch as we failed to find a difference in the frequency with which participants made a SS-RIF-consistent decision in the Test-Present and Test-Absent conditions, $\chi^2(1) = 0.097$, $p = 0.76$, we combined the data from these two conditions. Thirty-three out of 48 participants made RIF-consistent decisions, a proportion greater than chance (using a sign test, $p < 0.02$).

The second analysis offered a refinement over the first analysis, in that it examined whether SS-RIF-consistent decisions are more likely as SS-RIF impairment increased. We now focused solely on data from the Test-Present condition. We calculated the size of SS-RIF impairment [(Nrp) – (Rp−)] and the practice effect [(Rp+) – (Nrp)] and then used these scores in a binary logistic regression to test whether these two scores predicted SS-RIF-consistent decisions. We did not expect that the practice effect should make a contribution, inasmuch as the experiment was designed to make practice effects irrelevant. We did expect to see a contribution of SS-RIF impairment. Confirming the hypothesis, a binary logistic regression employing a forward conditional model excluded the practice effect, but included SS-RIF impairment as the only significant predictor, $\chi^2(1, N = 24) = 5.46$, $p < 0.02$; $\beta = 4.45$, odds ratio (OR) = 85.65, Wald = 4.01, $p < 0.05$.

GENERAL DISCUSSION

This study had two aims: (1) to determine whether SS-RIF can be observed as a consequence of reading information about a medical treatment, and (2) whether any observed SS-RIF can potentially affect subsequent decision-making. Regarding the first aim, both experiments clearly showed SS-RIF. As we noted in the introduction, the concurrent, covert retrieval underlying SS-RIF is optional. When a person reads about the advantages and disadvantages of treatments in a brochure, they do not need to remember silently any memories they have previously formed about the treatment. The current findings indicate that they do. Moreover, they retrieve what is mentioned in the brochure, but, as the presence of SS-RIF indicates, what they retrieve may inhibit the unmentioned related item. This finding underscores an important cost associated with selective presentation, even for medically relevant information.

As to the second issue addressed in this paper, the results indicate that socially shared RIF is a potential mechanism by which memory accessibility can affect decision-making, at least when the decision depends on the accessibility of precise information. By focusing on induced forgetting, our research adds substantially to previous efforts exploring how memory accessibility critically contributes to medical decision-making by exploring the effects of prior exposure on memory and on subsequent decisions (Redelmeier and Kahneman, 1996; Redelmeier et al., 2003; see also Baines et al., 1990; Erskine et al., 1990). To be sure, practice effects might also contribute, but the design of Experiment 2 eliminated any possible contribution of a practice effect, thereby highlighting the contribution of SS-RIF. How practice and induced forgetting might interact to lead to a final decision in situations where both

could play a role will, of course, depend on the relevance of the practiced and forgotten information to the target individual. There is no *a priori* reason to believe that practice effects trump the effects of induced forgetting. For instance, people may be aware of the role of practice and compensate for its influence when making the final decision. They are less likely to be aware of the role of induced forgetting, especially the different pattern of forgetting for unmentioned related over unrelated information. As a result, they might be less likely to adjust for the contribution of SS-RIF.

Several caveats are in order. We need to be cautious about making any general statement, inasmuch as we employed only one example of a disease. However, on the surface, there was nothing extraordinary about our description of Wheeler's Syndrome. When we asked our participants, in the debriefing phase, to indicate whether Wheeler's syndrome seems like something a friend might develop under some unfortunate circumstance, 97% responded in the affirmative. Moreover, we cannot be certain whether SS-RIF can drive decision-making if there is a substantial delay between selective practice and the final decision. Some studies suggest that impairment can last no more than 24 h (MacLeod and Macrae, 2001), whereas other studies find RIF after a week (Conroy and Salamon, 2006; Migueles and Garcia-Bajos, 2007; Tandoh and Naka, 2007; Garcia-Bajos et al., 2008; Storm et al., 2012). It is worth noting that even the shorter time frame may still be relevant to decision-making, especially if decision-making occurs in increments, with new or tentative decisions being made as new information is acquired (Johnson et al., 2005; Weber and Johnson, 2006).

In instances when the decision-maker has enough time to consider all advantages and disadvantages while reading a brochure or scanning the internet, selective retrieval might result in retrieval-induced facilitation for the unmentioned and related medical information (Chan et al., 2006). In these situations we suspect that treatment decisions will be driven by the resultant increase in accessibility. Future research should explore the effects of retrieval-induced facilitation, as well as the conditions that might induce facilitation over forgetting.

In the studies presented in this paper advantages always preceded disadvantages. The rationale for this decision was to avoid potential framing effects and to keep treatments' presentation as ecologically valid as possible. However, further research should also explore whether the order of presentation has a significant impact on RIF.

Finally, in these experiments, participants were asked to make a treatment decision for another individual. Memory accessibility may be impacted differently when the decision is made for self vs. for a significant other. There is some research to support this concern. For instance, decisions made for another individual can induce a higher sense of responsibility in the surrogate, resulting in a preference for more conservative options (Raymark, 2000). This observation, however, does not imply that SS-RIF would only play a role in surrogate decision-making. There is no *a priori* reason why it would also not apply to self-relevant decision.

The research provides a cautionary note about the risks of decision-driven selective retrieval of medical information. When exposed to medical information, like reading a brochure, talking with a doctor, or watching a commercial, the results here suggest that beyond a simple practice effect, selective remembering can induce forgetting for unmentioned, related, and relevant information. This induced forgetting could influence medical decision-making in not necessarily positive ways. When patients and significant others read incomplete information from brochures, Internet entries, or just simply listen to a commercial on the TV, these acts might, in the end, be more detrimental than informative for the decision-making process. A broad implication at the policy level of this research would be for medical providers to include complete and comprehensive information in pamphlets and Internet entries so that patients and their significant others are fully informed when making or advocating for medical decisions.

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REFERENCES

Anderson, M. C., Bjork, E. L., and Bjork, R. A. (2000). Retrieval-induced forgetting: evidence for a recall-specific mechanism. *Psychon. Bull. Rev.* 7, 522–530. doi:10.3758/BF03214366

Anderson, M. C., Bjork, R. A., and Bjork, E. L. (1994). Remembering can cause forgetting: retrieval dynamics in long-term memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 20, 1063–1087. doi:10.1037/0278-7393.20.5.1063

Anderson, M. C., and Levy, B. J. (2007). "Theoretical issues in inhibition: insights from research on human memory," in *Inhibition in Cognition*, eds D. S. Gorfein and C. M. MacLeod (Washington, DC: American Psychological Association), 81–102.

Anderson, M. C., and Spellman, B. A. (1995). On the status of inhibitory mechanisms in cognition: memory retrieval as a model case. *Psychol. Rev.* 102, 68–100. doi:10.1037/0033-295X.102.1.68

Baines, C. J., To, T., and Wall, C. (1990). Women's attitudes to screening after participation in the National Breast Screening Study. *Cancer* 65, 1663–1669. doi:10.1002/1097-0142(19900401)65:7<1663::AID-CNCR2820650735>3.0.CO;2-A

Barnier, A., Hung, L., and Conway, M. A. (2004). Retrieval-induced forgetting of autobiographical episodes. *Cogn. Emot.* 18, 457–477. doi:10.1080/0269993034000392

Beers, M. H., Porter, R. S., Jones, T. V., Kaplan, J. L., and Berkwits, M. (2006). *The Merk Manual of Diagnosis and Therapy*, 18th Edn. New Jersey: Merk Research Laboratories.

Boehmer, U., and Babayan, R. K. (2005). A pilot study to determine support during the treatment phase of early prostate cancer. *Psychooncology* 14, 442–449. doi:10.1002/pon.859

Chan, J. C. K., McDermott, K. B., and Roediger, H. L. (2006). Retrieval-induced facilitation: initially nontested material can benefit from prior testing of related material. *J. Exp. Psychol. Gen.* 135, 533–571. doi:10.1037/0096-3445.135.4.553

Coman, A., and Hirst, W. (2012). Cognition through a social network: the propagation of practice and induced forgetting effects. *J. Exp. Psychol. Gen.* 141, 321–336. doi:10.1037/a0025247

Coman, A., Manier, D., and Hirst, W. (2009). Forgetting the unforgettable through conversation: socially-shared retrieval-induced forgetting of September 11 memories. *Psychol. Sci.* 20, 627–633. doi:10.1111/j.1467-9280.2009.02343.x

Conroy, R., and Salamon, K. (2006). Talking about parts of a past experience: the impact of discussion style and event structure on memory for discussed and non-discussed information. *J. Exp. Child. Psychol.* 95, 278–297. doi:10.1016/j.jecp.2006.06.001

Cuc, A., Koppel, J., and Hirst, W. (2007). Silence is not golden: a case for socially-shared retrieval-induced forgetting. *Psychol. Sci.* 18, 727–733. doi:10.1111/j.1467-9280.2007.01967.x

Dodd, M. D., Castel, A. D., and Roberts, K. E. (2006). A strategy disruption component to retrieval-induced forgetting. *Mem. Cognit.* 34, 102–111. doi:10.3758/BF03193390

Erskine, A., Morley, S., and Pierce, S. (1990). Memory for pain: a review. *Pain* 41, 255–265. doi:10.1016/0304-3959(90)90002-U

Feldman, J. M., and Lynch, J. G. Jr. (1988). Self-generated validity and other effects of measurement on belief, attitude, intention and behavior. *J. Appl. Psychol.* 73, 421–435. doi:10.1037/0021-9010.73.3.421

Garcia-Bajos, E., Migueles, M., and Anderson, M. C. (2008). Script knowledge modulates retrieval-induced forgetting for eyewitness events. *Memory* 17, 92–103. doi:10.1080/09658210802572454

Gigerenzer, G., and Goldstein, D. G. (1996). Reasoning the fast and frugal way: models of bounded rationality. *Psychol. Rev.* 103, 650–669. doi:10.1037/0033-295X.103.4.650

Hirst, W., and Echterhoff, G. (2012). Remembering in conversations: the social sharing and reshaping of memory. *Annu. Rev. Psychol.* 63, 55–79. doi: 10.1146/annurev-psych-120710-100340

Iglesias-Parro, S., and Gomez-Ariza, C. J. (2006). Biasing decision-making by means of retrieval practice. *Eur. J. Cogn. Psychol.* 18, 899–908. doi:10.1080/09541440500501189

John, L. K., and Fischhoff, B. (2010). Changes of heart: the switch-value method for assessing value uncertainty. *Med. Decis. Making* 30, 388–397. doi:10.1177/0272989X09344750

Johnson, E. J., Haubl, G., and Keinan, A. (2007). Aspects of endowment: a query theory of value construction. *J. Exp. Psychol. Learn. Mem. Cogn.* 33, 461–474. doi:10.1037/0278-7393.33.3.461

Johnson, E. J., Steffel, M., and Goldstein, D. G. (2005). Making better decisions: from measuring to constructing preferences. *Health Psychol.* 24, S17–S22. doi:10.1037/0278-6133.24.4.S17

Lichtenstein, S., Slovic, P., Fischhoff, B., Layman, M., and Combs, B. (1978). Judged frequency of lethal events. *J. Exp. Psychol. Hum. Learn. Mem.* 4, 551–578. doi:10.1037/0278-7393.4.6.551

Lipitor Official Website. (2006). *In Lipitor (Atorvastatin Calcium)/Safety Info/Official Site.* Available at: http://www.lipitor.com/ [accessed January 19, 2012].

Loewenstein, G. (2005). Hot-cold empathy gaps and medical decision making. *Health Psychol.* 24, S49–S56. doi:10.1037/0278-6133.24.4.S49

Luce, M. F. (2005). Decision making as coping. *Health Psychol.* 24, S23–S28. doi:10.1037/0278-6133.24.4.S23

Lynch, J., and Srull, T. K. (1982). Memory and attentional factors in consumer choice. *J. Consum. Res.* 9, 18–37. doi:10.1086/208893

MacLeod, M. D., and Macrae, C. N. (2001). Gone but not forgotten: the transient nature of retrieval-induced forgetting. *Psychol. Sci.* 12, 148–152. doi:10.1111/1467-9280.00325

Macrae, C. N., and Roseveare, T. A. (2002). I was always on my mind: the self and temporary forgetting. *Psychon. Bull. Rev.* 9, 611–614. doi:10.3758/BF03196320

Menon, G., and Raghubir, P. (2003). Ease-of-retrieval as an automatic input in judgments: a mere accessibility framework? *J. Consum. Res.* 30, 230–243. doi:10.1086/376804

Migueles, M., and Garcia-Bajos, E. (2007). Selective retrieval and induced forgetting in eyewitness memory. *Appl. Cogn. Psychol.* 21, 1157–1172. doi:10.1002/acp.1323

Moxey, A., O'Connell, D., McGettigan, P., and Henry, D. (2003). Describing treatment effects to patients. How they are expressed makes a difference. *J. Gen. Intern. Med.* 18, 948–959. doi:10.1046/j.1525-1497.2003.20928.x

Raymark, P. H. (2000). Accepting or rejecting medical treatment: a comparison of decisions made for self versus those made for a significant other. *J. Appl. Soc. Psychol.* 30, 2409–2436. doi:10.1111/j.1559-1816.2000.tb02443.x

Redelmeier, D., and Kahneman, D. (1996). Patients' memories of painful medical treatments: real-time and retrospective evaluations of two minimally invasive procedures. *Pain* 66, 3–8. doi:10.1016/0304-3959(96)02994-6

Redelmeier, D. A., Katz, J., and Kahneman, D. (2003). Memories of colonoscopy: a randomized trial. *Pain* 104, 187–194. doi:10.1016/S0304-3959(03)00003-4

Reyna, V. F. (2008). A theory of medical decision making and health: fuzzy trace theory. *Med. Decis. Making* 28, 850–865. doi:10.1177/0272989X08327066

Reyna, V. F., and Hamilton, A. J. (2001). The importance of memory in informed consent for surgical risk. *Med. Decis. Making* 21, 152–155. doi:10.1177/0272989X0102100209

Reyna, V. F., and Lloyd, F. (2006). Physician decision making and cardiac risk: effects of knowledge, risk perception, risk tolerance, and fuzzy processing. *J. Exp. Psychol.* 12, 179–195.

Simon, H. A. (1985). Human nature in politics: the dialogue of psychology with political science. *Am. Polit. Sci. Rev.* 79, 293–304. doi:10.2307/1956650

Srirangam, S. J., Pearson, E., Grose, C., Brown, S. C., Collins, G. N., and O'Reilly, P. H. (2003). Partner's influence on patient preference for treatment in early prostate cancer. *Br. J. Urol. Int.* 92, 365–369. doi:10.1046/j.1464-410X.2003.04355.x

Stone, C. B., Barnier, A. J., Sutton, J., and Hirst, W. (2010). Building consensus about the past: schema consistency and convergence in socially-shared retrieval-induced forgetting. *Memory* 18, 170–184. doi:10.1080/09658210903159003

Storm, B. C., Bjork, E. L., and Bjork, R. A. (2005). Social metacognitive judgments: the role of retrieval-induced forgetting in person memory and impressions. *J. Mem. Lang.* 52, 535–550. doi:10.1016/j.jml.2005.01.008

Storm, B. C., Bjork, E. L., and Bjork, R. A. (2012). On the durability of retrieval-induced forgetting. *J. Cogn. Psychol. (Hove)* 24, 617–629. doi:10.1080/20445911.2012.674030

Storm, B. C., Bjork, E. L., Bjork, R. A., and Nestojko, J. (2006). Is retrieval success necessary for retrieval-induced forgetting? *Psychon. Bull. Rev.* 13, 1023–1027. doi:10.3758/BF03213919

Storm, B. C., and Levy, B. J. (2012). A progress report on the inhibitory account of retrieval-induced forgetting. *Mem. Cognit.* 40, 827–843. doi:10.3758/s13421-012-0211-7

Tandoh, K., and Naka, M. (2007). Durability of retrieval-induced forgetting. *Jpn. J. Psychol.* 78, 310–315. doi:10.4992/jjpsy.78.310

Tversky, A., and Kahneman, D. (1973). Availability: a heuristic for judging frequency and probability. *Cogn. Psychol.* 5, 207–232. doi:10.1016/0010-0285(73)90033-9

Weber, E. U., and Johnson, E. J. (2006). "Constructing preferences from memories," in *The Construction of Value*, eds S. Lichtenstein and P. Slovic (New York: Cambridge University Press), 397–410.

Wixted, J. T. (2004). The psychology and neuroscience of forgetting. *Annu. Rev. Psychol.* 55, 235–269. doi:10.1146/annurev.psych.55.090902.141555

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The beneficial effect of testing: an event-related potential study

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The enhanced memory performance for items that are tested as compared to being restudied (the testing effect) is a frequently reported memory phenomenon. According to the episodic context account of the testing effect, this beneficial effect of testing is related to a process which reinstates the previously learnt episodic information. Few studies have explored the neural correlates of this effect at the time point when testing takes place, however. In this study, we utilized the ERP correlates of successful memory encoding to address this issue, hypothesizing that if the benefit of testing is due to retrieval-related processes at test then subsequent memory effects (SMEs) should resemble the ERP correlates of retrieval-based processing in their temporal and spatial characteristics. Participants were asked to learn Swahili-German word pairs before items were presented in either a *testing* or a *restudy* condition. Memory performance was assessed immediately and 1-day later with a cued recall task. Successfully recalling items at test increased the likelihood that items were remembered over time compared to items which were only restudied. An ERP subsequent memory contrast (later remembered vs. later forgotten tested items), which reflects the engagement of processes that ensure items are recallable the next day were topographically comparable with the ERP correlate of immediate recollection (immediately remembered vs. immediately forgotten tested items). This result shows that the processes which allow items to be more memorable over time share qualitatively similar neural correlates with the processes that relate to successful retrieval at test. This finding supports the notion that testing is more beneficial than restudying on memory performance over time because of its engagement of retrieval processes, such as the re-encoding of actively retrieved memory representations.

Keywords: episodic memory, testing effect, ERP, reinstatement, memory retrieval

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Introduction

The testing effect refers to those findings which indicate that testing a studied list leads to better memory performance in a final test than restudying the list. In other words, testing is not only an assessment of memory, but also a way to change memory and consequently researchers have suggested that testing should be used as an efficient learning strategy (for review, see Roediger and Karpicke, 2006; Karpicke et al., 2014). The majority of experiments on this topic are behavioral studies, whilst the neuronal underpinning of the testing benefit has been addressed only recently (Eriksson et al., 2011; van den Broek et al., 2013; Wing et al., 2013; Rosburg et al., 2015). In the current study, we explored learning-by-testing mechanisms by analyzing the electrophysiological correlates of successful encoding during testing using a subsequent memory paradigm.

The beneficial effect of testing on memory is thought to come about because of the consequences of repeatedly retrieving information (Roediger and Butler, 2011). Researchers often refer to this process as retrieval practice, which in turn is thought to be able to contribute to memory via several mechanisms. For example, more effort might be allocated to items during testing than during restudy, which leads to enhanced reprocessing of information (Pyc and Rawson, 2009). Additionally, according to the transfer appropriate processing account, similar processes initiated during testing as for those required in the final memory test make the material more accessible in the final test (McDaniel et al., 1989; McDaniel and Fisher, 1991). Furthermore, testing requires the retrieval of information from memory. Retrieval processes may cause semantically-related information to be generated in a way that elaborates the retrieval cue as well as strengthening the relation between cue and target (Carpenter and DeLosh, 2006; Carpenter, 2009, 2011). Encoded information consequently becomes easier to access during the final test (Bjork, 1975; McDaniel and Masson, 1985).

In a recent review, Karpicke et al. (2014) analyzed the conditions under which retrieval practice has shown a memory advantage compared to restudy. Several principles of retrieval-based learning were summarized in the episodic context account. The core assumption is that retrieval practice places participants into a retrieval mode in which they attempt to reconstruct the past and to reinstate the temporal context. This retrieval process causes the item to be updated within its context, such that it may become associated with multiple context cues after extended retrieval practice, making it more retrievable as a consequence. Karpicke et al. (2014) provide empirical evidence for this hypothesis by showing that source memory decisions during testing led to better performance in a final recall test than old-new recognition memory decisions, whereas both conditions were better than an elaboration (forming images or generating word associates) condition. According to most dual process models of recognition memory, two distinct retrieval processes serve recognition: an automatic familiarity process and a slower more effortful recollection process (Yonelinas et al., 2010). Critically, whereas both processes can support simple item recognition, only recollection can afford the reinstatement of an item in its context (e.g., Diana et al., 2007). If the effect of retrieval practice on later memory performance improvement is due to the reinstatement of the prior episodic context, neural correlates of recollection should be most pronounced at the time point when retrieval practice is actively engaged. Important to consider is that, although recollection may incidentally occur during restudy, it is likely to occur less often than during retrieval practice, because recollection is generally considered an effortful process (Jacoby, 1991, 1998) which requires the engagement of retrieval mode and is not explicitly demanded by the restudy task. Subsequently, expectations derived from the episodic context account would specify that recollection processes should be evident under retrieval practice conditions, yet negligible during restudy.

In line with the accounts reviewed above, functional neuroimaging studies have recently provided evidence for the notion that testing benefits memory performance by recruiting retrieval processes. These studies have all employed versions of the subsequent memory paradigm (Davachi et al., 2001; Paller and Wagner, 2002). After an initial study phase (Phase 1), items were either restudied or tested in Phase 2, and during this period brain activity was measured. A final test (Phase 3) followed after some duration to assess memory performance. To disclose processes during testing or restudy condition, and to relate it with successful memory performance in a later test, items presented in Phase 2 were sorted into those that were subsequently remembered or forgotten in Phase 3. Brain activity locked to remembered items is usually then contrasted with forgotten items in order to capture subsequent memory effects (SMEs) and determine whether they differ for the two conditions.

In one such study, Wing et al. (2013) asked participants to learn pairs of weakly associated nouns and then tested them on these a day later. In the testing condition, activity in the hippocampus, left middle temporal cortex and medial prefrontal cortex was larger to subsequently remembered than forgotten items. Additional connectivity analyses revealed increased coupling between the hippocampus and ventrolateral prefrontal cortex, medial pre-frontal cortex, and posterior cingulate cortex in the testing condition. The activation in the middle temporal lobe, especially the hippocampus is taken to reflect relational memory processes. Relational processes enable recollection by binding disparate information into coherent representations during retrieval. Hence, during retrieval practice these processes are taken to strengthen the previously learned word-word associations or generate new associations that provide additional retrieval cues and improve retention in the final memory test (Wing et al., 2013).

In another study, van den Broek et al. (2013) asked participants to learn the Dutch translations of Swahili words. Participants practiced all the items three times through three repeated restudy/testing blocks in Phase 2 and the final test followed after 1 week. Activity was greater in the inferior frontal gyrus, midbrain and ventral striatum in the testing compared to the restudy condition, which was taken as evidence for higher cognitive control and modulation of memory by striatal reward circuits during testing. Critically, activity in left inferior parietal and left middle temporal areas predicted recall in the final memory test in the testing but not the restudy condition. The activity in the left inferior parietal and left middle temporal areas were modulated by the amount of information retrieved with higher activity during testing of subsequently remembered than forgotten words. As both areas have been consistently found to be involved in successful memory retrieval (Diana et al., 2007; Vilberg and Rugg, 2008) or the allocation of attention to retrieved information (Cabeza et al., 2008; Hutchinson et al., 2014), this study provides additional support for the view that testing involves the reinstatement of a prior study context by enhancing recollective or relational processing.

These two fMRI studies thus provide general support for the retrieval account of the testing effect, in which testing should cause retrieval of prior encoded episodes and a reinstantiation of the item in its context. This update of the memory trace during testing may provide additional cues for the final memory test. Comparable electrophysiological evidence is scarce, however,

and the current study was designed to address this gap in the literature. Electrophysiological data is likely to be useful for understanding the mechanisms underlying the testing effect not only because of its greater temporal resolution, but also because decades of work using the event-related potential (ERP) technique in recognition tests have revealed a family of old/new effects thought to map onto distinct retrieval processes (for reviews see Friedman and Johnson, 2000; Mecklinger, 2000; Rugg and Curran, 2007). One such effect is usually referred to as the left-parietal old/new effect. Behavioral conditions that modulate recollection also modulate the left-parietal old/new effect and this effect has been shown to correlate with recollection-based memory judgments in item and associative memory studies (Friedman and Johnson, 2000). The temporal resolution of the ERP technique allows us to capture a recollection process at the time when the items were tested and prior studies have shown that the left-parietal old/new effect, the ERP correlate of recollection is most pronounced between approximately 500 and 700 ms after stimulus onset (Friedman and Johnson, 2000; Rugg and Curran, 2007). This electrophysiological marker of recollection thus allows for the exploration of a core prediction derived from the episodic context account outlined above: that recollection processes occur disproportionately more in testing than restudy conditions and it is this process which is associated with superior downstream memory performance for retrieval practice. This would be demonstrated if the electrophysiological subsequent memory effect (SME) in the testing condition but not in the restudy condition, was found to resemble the left-parietal old/new index of recollection.

To date, few ERP recognition studies have explored the electrophysiological consequences of testing. Rosburg et al. (2015) examined ERP correlates of immediate one-time testing in a source memory task. After initial learning, half of the learned items were presented in a source memory test before all old items were presented within a final old/new test. This allowed items that were studied and tested to be contrasted with those which were only studied once. Testing led to better item and source memory as well as speeded reaction times. The left parietal old/new effect in the final test was enhanced for items that were tested immediately after first-time study. In earlier work, the left-parietal old/new effect has been shown to correlate with the amount of retrieved information (Vilberg et al., 2006). In line with this, Rosburg and colleagues' results were taken as a demonstration that the one-time testing allows more detailed information recollected from the prior study episode. Although the data reported by Rosburg and colleagues clearly show the downstream impact of testing on recognition processes in the form of a boosted left parietal old/new effect, the electrophysiological correlates of processes engaged at the time of testing in contrast to a restudy condition using a subsequent memory paradigm have not yet been reported.

Another ERP effect that is frequently reported in recognition memory studies is the late posterior negativity (LPN). The LPN is a late and posteriorly distributed ERP component that is observed mainly in source recognition studies (Johansson and Mecklinger, 2003). It onsets around the time recognition decisions are given and is thought to reflect the assessment and evaluation of information retrieved from memory in situations in which memory features cannot easily be recovered. The LPN is most pronounced when extended retrieval processing is required, for example in situations in which multi-featured memory traces have to be discriminated (Leynes and Kakadia, 2013) or when the to-be-discriminated memory traces are weak or overlapping (Rosburg et al., 2011).

In the current study, participants studied Swahili-German word pairs in Phase 1. During Phase 2, pairs were either tested or restudied whilst EEG was recorded. The final test (Phase 3) followed 1 day later to increase the likelihood of observing a substantial testing effect (Butler and Roediger, 2007; Karpicke and Roediger, 2008). The main prediction for the behavioral results was that pairs tested in Phase 2 should be better remembered in Phase 3 than pairs that were restudied in Phase 2. For the ERP results, we expected subsequent memory effects (SMEs) for both studied and tested pairs in Phase 2. However, it was predicted that the SME during testing should differ qualitatively from the SME during restudy if distinctive retrieval processes are engaged in the two conditions. If retrieval practice promotes learning by the recruitment of recollection-like processes we expected the SME for tested items to resemble the late parietal old/new effect, i.e., the putative ERP correlate of recollection. The ERP correlate of recollection was assessed by contrasting the ERP response to items correctly recalled in Phase 2 but not in Phase 3, with those elicited by items which were neither recalled in Phase 2 and Phase 3 (see **Table 1**). If the LPN is related to the assessment of retrieved information, it is hypothesized that the LPN will be observed in the testing condition in which extended retrieval processing is required but not in the restudy condition in which retrieval does not take place. At the same time, we also expected the LPN to covary with the testing conditions, with the largest LPN in those testing trials in which knowledge from a prior study episode is not readily recovered in either Phase 2 or in Phase 3 and thus for which it is assumed that the resulting evaluation demands are high.

Methods

Participants

Twenty-six students enrolled at University of Saarland gave informed consent prior to participation. Participants were compensated with either course credit or cash (8€/h). An

TABLE 1 | Condition labels categorized by experimental conditions and Memory Condition at three time points.

Practice condition	Phase 2 practice	Day1 recall	Phase 3 Day2 recall	Condition label
Restudy		R	R	SR
		R	F	SF
Testing	R	R	R	RR
	R	R	F	RF
	F	F	F	FF

R, Remember; F, Forgotten; S, restudy.

additional 10€ were given to the top 25% performers based on their performance at final recall. All participants were right-handed (Oldfield, 1971), reported no history of neurological disorders and had normal or corrected vision. The study was approved by the Ethic Committee of the Social and Applied Human Sciences of Saarland University. Two participants did not participate in all sessions, three had very poor performance (less than 25% correct at Day 1 recall), one had already participated in a similar experiment, and five had to be excluded due to insufficient artifact-free trials for ERP analysis (<16 trials). Fifteen participants thus entered the final analysis (aged 20–28 years old, $M = 22.87$, $SD = 2.00$).

Materials

Stimuli were 220 Swahili-German word-pairs for which the German words had a frequency of between 10 and 100 occurrences per million (Mannheim frequency per Million; Baayen et al., 1995). All words referred to touchable nouns. Swahili words were translations of the German target words. Where no equivalent translation was available from online dictionaries, a near-synonym or a related-norm was selected. Prenasalized consonants in Swahili (e.g., "mv") which are difficult for German readers to pronounce were kept to a minimum. Word length was matched so that on average both Swahili and German words were 6-letters long. A complete list of stimuli is available in Supplementary Table 1.

Design Overview

The experiment consisted of two sessions separated by 1 week. Each session comprised five cycles (each consisting of Phases 1 and 2) and a 2-day final recall (Phase 3). In each cycle participants studied 22 word-pairs. In the final test all 110 word-pairs studied on the previous day were tested (see **Figure 1A**). During the initial learning phase, word-pairs were presented three times in randomized order. Phase 2—during which EEG was recorded—followed initial learning. In Phase 2, 11 word-pairs were restudied again whereas the remaining 11 word-pairs of the study list were tested. Additionally, at the end of each cycle all 22 word-pairs were tested in a cued recall task (Day 1 recall). In this test, only Swahili words were presented as cues and participants had to retrieve the associated German words. Participants processed five of these study cycles on Day 1. Approximately 20∼28 h later, participants returned for the final cued recall test (hereafter, Day 2 recall). To obtain sufficiently large trial numbers for the ERP analyses, the same procedure was repeated a week later with a different set of stimuli. In total, participants processed 110 items in the restudy and 110 items in the testing condition.

Procedure

Each session began with the application of the electrode cap. All instructions were given both verbally and were shown on the computer screen at the beginning of the actual experiment. Participants began with a practice session comprising six word-pairs to familiarize them with the task procedure. As illustrated in **Figure 1B**, in each learning phase, word-pairs were

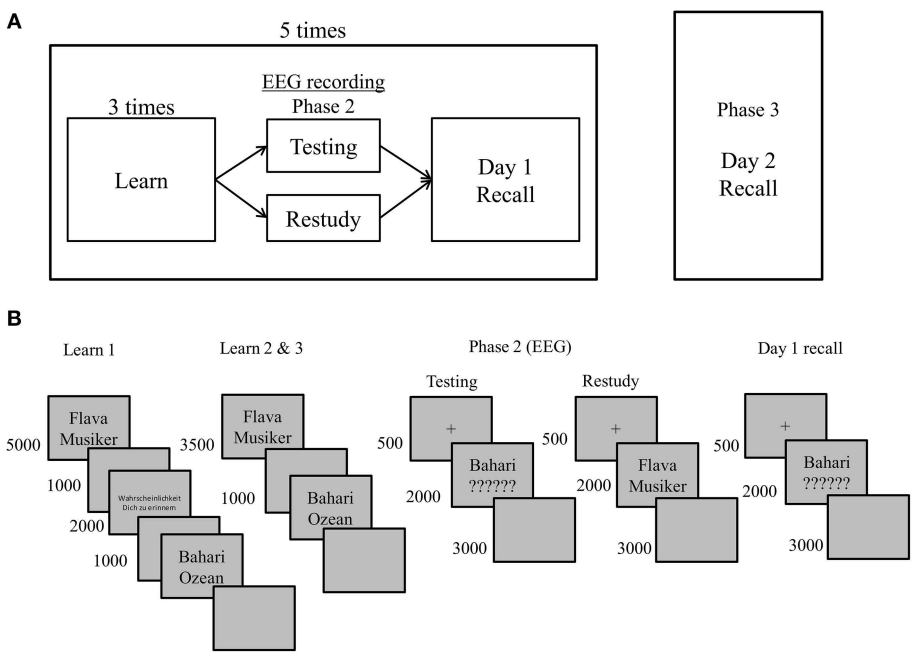


FIGURE 1 | (A) Illustration of the procedure realized in each session. **(B)** Procedure for one cycle on Day 1. Five such cycles each consisting of 22 different items were run on Day 1. The procedure of the final cued recall test on Day 2 was identical to Day 1 recall except for a longer response deadline to 6000 ms and the testing of all 110 items, which is not illustrated in this figure. Note that in Phase 2 (the EEG session) participants did not respond before the offset of the restudy or testing cues which were presented for 2000 ms, respectively.

presented in black against a gray background for 5000 ms on the display followed by a 1000 ms blank screen. Participants were encouraged to memorize word-pairs during this time. Participants were asked to judge how likely it was that they would remember the word-pair after the first presentation of each word-pair. They were instructed to use the right index finger to make a judgment of learning (JOL) on a 5-step scale where 1 means "definitely forget," 2 "probably forget," 3 "unsure," 4 "probably remember," and 5 "definitely remember" (Skavhaug et al., 2010). This judgment was given when "Wahrscheinlichkeit Dich zu erinnern" ("likelihood that you will remember") was displayed. The JOL trial terminated when an answer was given or after 2000 ms, and was followed by a 1000 ms blank screen. The JOL data will not be reported here. After initial learning trials were completed for all 22 word-pairs within a cycle, participants studied the same list of word-pairs two more times in randomized order, but no JOL was required for second and third learning presentations. The presentation time of the word-pairs was 3500 ms followed by a 1000 ms blank screen.

In Phase 2, 50% of the word-pairs were presented in the testing condition whilst the remainder of the pairs was restudied. The assignment of items to testing/restudy condition was counterbalanced across participants. In the testing condition, participants saw Swahili words above six question marks for 2000 ms and were required to recall the German words. At the offset of the stimuli, they were required to say the German translation for the Swahili word aloud within the 3000 ms deadline. In the restudy condition, participants saw the Swahili-German pairs for a fourth time for 2000 ms. Participants were required to say the German words aloud once the stimuli were removed from the screen within the 3000 ms deadline. Testing and restudy trials were blocked to minimize task-switching demands and the order of testing vs. restudy trials was counterbalanced across participants. At the end of each cycle, a Day 1 cued recall task was completed for the 22 word-pairs. Times of presentation and response requirements were identical to testing condition trials. Participants took a self-paced break and proceeded to the next cycle. Each session took approximately 1 h.

Approximately 20∼28 h later, participants returned to complete Day 2 cued recall test where all the 110 word pairs from the preceding day were tested. Each trial began with a 500 ms fixation cross and a 2000 ms presentation time with Swahili cue word and six question marks. Afterwards, participants had 6000 ms to provide a response for each Swahili word cue. The task lasted approximately 20 min. All responses were recorded via a microphone throughout. Correct and incorrect responses were coded online by an experimenter. No EEG was recorded during the final test.

EEG Acquisition and Analysis

Fifty-eight Ag/AgCI electrodes were embedded in an elastic cap (Easycap, Herrsching, Germany) based on the extended international 10–20 system. The electroencephalogram (EEG) was recorded continuously with a sampling rate of 500 Hz. Two additional pairs of electrodes were used: one pair was placed on the outer canthi for horizontal EOG. Another two electrodes were placed above and below the right eye for vertical EOG, respectively. An electrode placed anterior to Fz served as the ground. EEG was referenced online to the left mastoid. The impedances of the recording electrodes were kept below 5 kΩ. Data was recorded online and processed offline by commercial software Brain Vision Recorder and Analyzer (Brain Products). EEG signals were recorded with a digital bandpass filter (DC-70 Hz) at a rate of 500 Hz with an extra filter applied offline (0.03–30 Hz, 12 dB/oct). Final epochs extended from 100 ms prestimulus until 1000 ms after stimulus presentation during Phase 2. Data were downsampled to 250 Hz and offline re-referenced to the average of the mastoid signals. Baseline correction started from 100 ms before stimulus onset to stimulus onset. A correction algorithm based on independent component analysis (ICA) was employed for EOG artifact rejection (Makeig et al., 2004).

ERP waveforms were created for five conditions (see **Table 1**). ERPs to restudied items are labeled as "studied later-remembered (SR)" or "studied later-forgotten (SF)" pairs, depending upon whether they were recalled correctly on Day 2. Tested items were separated into three categories. Tested items recalled correctly at Phase 2 and on Day 2 were labeled as "remember-remember (RR)"; tested items recalled correctly at Phase 2, but forgotten on Day 2 are labeled as "remember-forgotten (RF)"; and tested items which were not correctly retrieved at either Phase 2 or on Day 2 are labeled as "forgotten-forgotten (FF)." The mean number and range (in parenthesis) of trials entering into each individual's average were as follows: 35 (16–53) SR; 39 (26–51) SF; 37 (21–57) RR; 30 (16–43) RF; 34 (16–54) FF.

ERP analyses are based on the following contrasts: (i) the SME for restudied items was revealed by contrasting SR and SF; (ii) the SME for tested items was revealed by contrasting RR and RF; (iii) the ERP correlate of immediate-retrieval was assessed by contrasting RF and FF which should isolate immediate retrieval success during Phase 2 for tested items. The comparison between this contrast and the SME for tested items [contrast (ii)] in the 500–700 ms time interval in which the ERP correlate of recollection can reliably be recorded was used to test whether correct recall on Day 2 is associated with the ERP correlate of recollection. The fourth contrast (iv) was between ERPs to studied items (collapsed across SR and SF) and ERPs to RR, RF, and FF pairs, to test whether the LPN is elicited solely by tested items and if so, whether it is modulated by the ease with which memory representations are retrievable. This fourth contrast was specifically tested in the last time window 700–1000 ms due to the fact that the onset of LPN found in previous studies is usually later than the time window of recollection.

ANOVAs were used to test mean amplitude differences for each condition (i.e., SR, SF; RR, RF, FF) from three selected time windows: 300–500, 500–700, and 700–1000 ms. These time windows were chosen because the effects of interest were present in the time intervals and because they correspond with those time intervals used for the conventional analysis of ERP memory encoding and retrieval studies. The 300–500 ms window covers that in which an early mid-frontal old/new effect often associated with familiarity is usually reported. The 500–700 ms time window was selected to capture the left-parietal old/new effect.

Additionally, the LPN is usually not observed before 700 ms after onset of a retrieval cue and extends for several 100 ms (Johansson and Mecklinger, 2003) and thus the 700–1000 ms time window was used to capture this effect. Consistent with other ERP studies exploring encoding and retrieval processes (Bader et al., 2010; Halsband et al., 2012), mean amplitudes were taken from three frontal (F3, Fz, F4), three central (C3, Cz, C4), and three parietal (P3, Pz, P4) electrodes, chosen because they best represent the scalp and should allow detection of frontally-extended SMEs as well as the left-parietal effect and the LPN. Repeated measures ANOVAs included the factors Memory Condition (see Result Section for the factors levels used in the four contrasts) and 3 Anterior-Posterior (frontal, central, parietal) and 3 Laterality (left [3], middle [z], right [4]). Degrees of freedom were adjusted for the ANOVAs by incorporating the Greenhouse-Geisser correction for violations of sphericity when appropriate. The adapted degrees of freedom are reported for both behavioral and ERP data.

Results

Behavioral Data

Figure 2 shows mean proportions of correct recall for the testing/restudy conditions on Day 1 and Day 2. As revealed by a Shapiro-Wilk test for normality (Shapiro and Wilk, 1965) all four mean proportion scores were normally distributed ($p > 0.10$). An ANOVA with factors testing/restudy condition and time (Day 1, 2 recall) revealed a main effect of time, $F_{(1, 14)} = 298.90$, $p < 0.01$ and an interaction between testing/restudy conditions and time, $F_{(1, 14)} = 33.39$, $p < 0.01$. To follow up the interaction effect, we compared the amount of recalled items between testing and restudy conditions on Day 1 and Day 2, respectively. The result showed that on Day 1 more restudied items ($M = 0.68$, $SD = 0.13$) were recalled than tested items ($M = 0.62$, $SD = 0.10$), $t_{(14)} = -2.31$, $p < 0.05$, while on Day 2 this difference was reversed. A marginally significant testing effect was found on Day 2 where participants were able to recall more tested items ($M = 0.35$, $SD = 0.09$) than restudied items ($M = 0.32$, $SD = 0.11$), $t_{(14)} = 1.79$, $p = 0.10$. In addition, the difference in the amount of correctly recalled items from Day 1 to Day 2 is significantly smaller in testing (Mean difference from Day 1 to Day 2 = 0.27, $SD = 0.06$) than in the restudy condition (Mean difference from Day 1 to Day 2 = 0.36, $SD = 0.09$), $t_{(14)} = -5.78$, $p < 0.01$. This suggests that, once successfully recalled in Phase 2, tested items were less likely to be forgotten on Day 2 in comparison to merely restudied items. This benefit of testing from Day 1 to Day 2 recall allowed us to proceed with the ERP analysis to explore the neural underpinnings of this behavioral testing effect and its relevance on later memory performance as presented in the following.

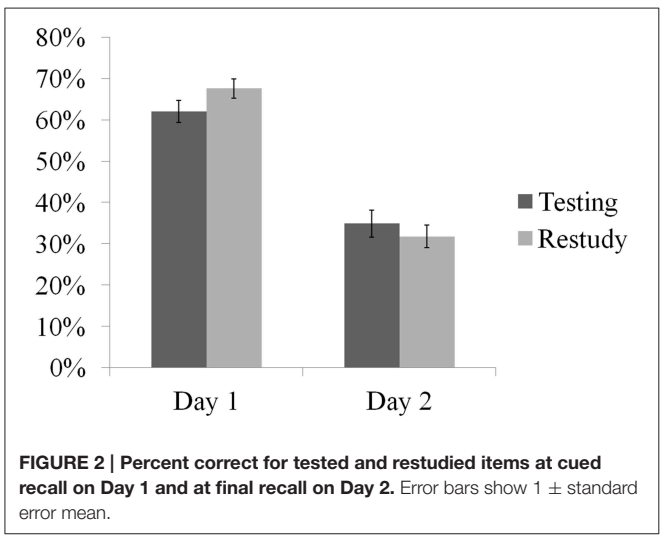


FIGURE 2 | Percent correct for tested and restudied items at cued recall on Day 1 and at final recall on Day 2. Error bars show 1 ± standard error mean.

ERP Data

Restudy Condition

This analysis compared ERPs elicited by restudied items that were either remembered or forgotten on Day 2 recall [contrast (i): Restudy SME]. As shown in **Figure 3A**, small differences from 300 to 500 ms at posterior sites were observed; however, a global ANOVA with the factors Memory Condition (SR/SF: later remembered/later forgotten) × 3 AP × 3 Laterality in the three selected time windows did not reveal any main effect of Memory Condition nor any interaction effect including this factor (See **Table 2A**). There were thus no significant ERP differences in the restudy condition of Phase 2 between items that were remembered or forgotten on the Day 2 recall test. Given this null effect and to make the remainder of the analyses more accessible,

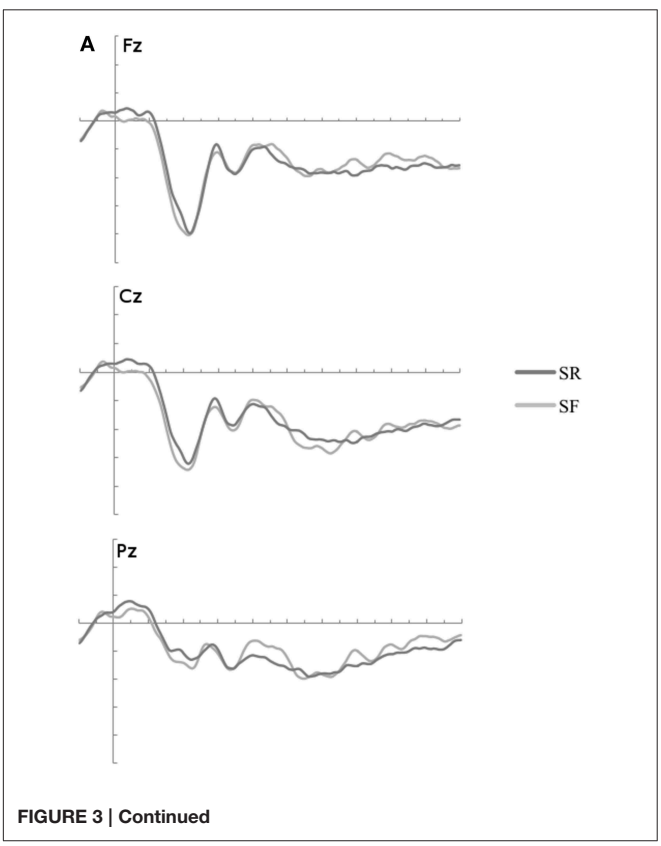


FIGURE 3 | Continued

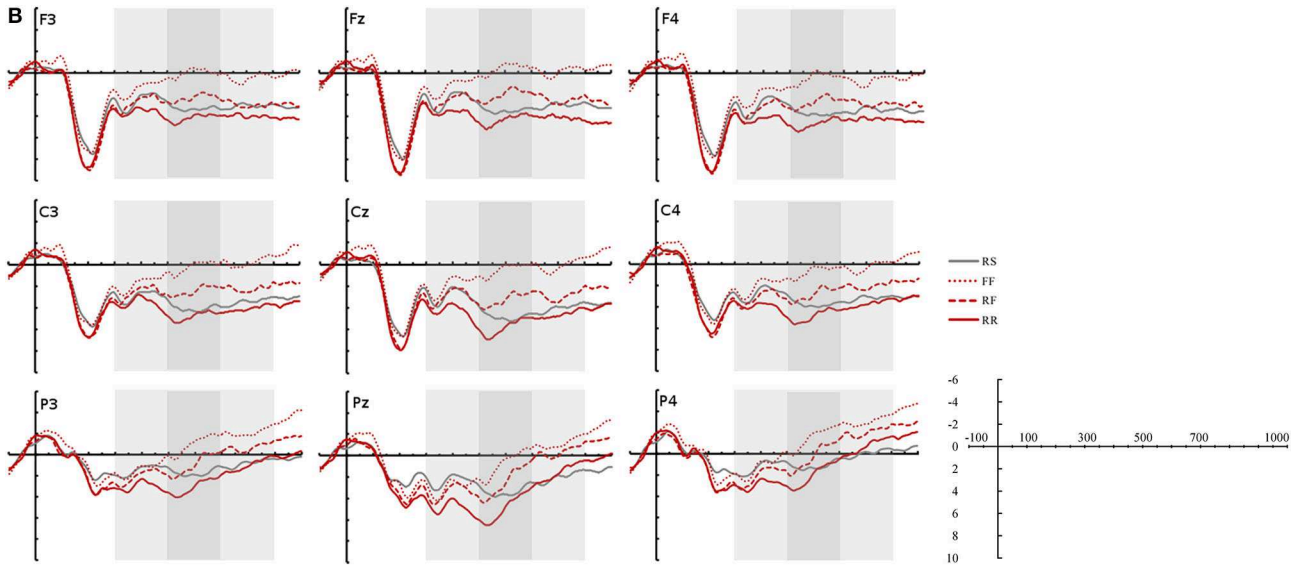


FIGURE 3 | (A) The ERP waveforms to restudied items which were later remember and forgotten (SR/SF) were not significantly different at any time windows of interest. **(B)** ERP waveforms to all restudied items (RS) and tested items categories by Memory Condition (RR, RF, FF). ERPs are plotted from 100 ms before stimulus onset to 1000 ms thereafter at frontal, central and posterior midline sites: Fz, Cz, and Pz. Three time windows of interest are marked in gray. The waveforms were low-passed filtered at 12 Hz for illustration. RR, remembered; RF, later forgotten; FF, immediately forgotten.

the two restudy conditions (SR/SF) were collapsed into one RS condition for the remainder of the relevant analyses.

Testing Condition

Corresponding degrees of freedom, *F*- and *p*-values for contrasts related to the items in the testing condition are reported in **Table 2**.

SME for tested items

As shown in **Figure 3B**, the ERPs to RR items start to diverge from ERPs to RF items around 300 ms post-stimulus, with a greater relative positivity for RR items. This difference is widely distributed across the scalp (see **Figure 4** upper panel). A global ANOVA with factors of Memory Condition (RR/RF) × 3 AP × 3 Laterality revealed a main effect of subsequent memory in all three time windows of interest from 300–500, 500–700 to 700–1000 ms. No interaction between the Memory Condition factor and other factors was found in either time interval.

ERP correlates of immediate-retrieval

The waveforms to RF and FF in **Figure 3B** show that the ERPs to immediately-remembered items were more positive-going than to forgotten items. Even though visual inspection of the waveforms suggest that the waveforms for RF and FF begin to diverge at round 300 ms, no reliable effect involving the Memory Condition factor were found in the early (300–500 ms) time interval (see **Table 2**). Reliable differences between the RF and FF condition, however, start at 500 ms and on the basis of visual inspection (**Figure 4** lower panel), this effect appears to be more frontal-central than posterior, particularly in the late time window (700–1000 ms). ANOVAs with factors of Memory Condition (RF/FF) × 3 AP × 3 Laterality revealed a main effect of Memory Condition in the 500–700 ms time window. In the 700–1000 ms time window, there was an interaction between Memory Condition and AP. Bonferroni adjusted follow-up tests (with the critical α-level set to $p = 0.02$) with factors of Memory Condition (RF/FF) for each of the 3 levels of AP (frontal, central or posterior) revealed that the main effect of Memory Condition was not significant neither at frontal ($p > 0.04$) nor at central ($p < 0.05$) or posterior sites ($p < 0.21$).

Comparing the SME and immediate-retrieval effect

Our main prediction was that if retrieval practice promotes learning by the recruitment of recollection-like processes, the SME for tested items should resemble the ERP correlate of immediate retrieval (as reflected in the RF/FF contrast). To directly test this, we examined whether the immediate-retrieval effect and the SME in the 500–700 ms time window in which the ERP correlate of recollection can reliably be recorded differ in scalp topography, as would be expected if different neuronal circuitries have contributed to both effects. To improve the sensitivity of this contrast, all 58 recording sites were included in this analysis. An additional analysis was conducted on amplitude normalized mean values to ensure that any differences in scalp topography between the two conditions do not result from amplitude differences (McCarthy and Wood, 1985). The ANOVA with factors Memory condition (RR-RF; RF-FF) and recording site did not reveal a significant interaction, [non-scaled data: $F_{(57, 798)} = 0.66$, $p = 0.98$; scaled data: $F_{(57, 798)} = 0.68$, $p = 0.97$], suggesting that highly similar brain circuitries were active in the immediate-retrieval processes and the 500–700 ms proportion of the SME contrast.

TABLE 2 | ANOVA table for (A) Restudy SME, Test SME, and Immediate retrieval effect (B) LPN analyses.

(A)					(B)		
Contrast	**Effect**	**300–500**	**500–700**	**700–1000**	**Contrast**	**Effect**	**700–1000**
(i) Restudy subsequent memory effect					(iv) LPN		
SR/SF	Condition	n.s.	n.s.	n.s.	RS/RR	Condition	n.s.
	... × AP	n.s.	n.s.	n.s.		... × AP	$F_{(1.26,\ 17.61)} = 4.33,\ p < 0.05$
	... × LAT	n.s.	n.s.	n.s.		... × LAT	n.s.
	... × AP × LAT	n.s.	n.s.	n.s.		... × AP × LAT	n.s.
(ii) Test subsequent memory effect					RS/RF	Condition	n.s.
						... × AP	n.s.
RR/RF	Condition	$F_{(1,\ 14)} = 5.35,\ p < 0.05$	$F_{(1,\ 14)} = 14.26,\ p < 0.01$	$F_{(1,\ 14)} = 6.21,\ p < 0.05$		... × LAT	n.s.
	... × AP	n.s.	n.s.	n.s.		... × AP × LAT	n.s.
	... × LAT	n.s.	n.s.	n.s.	RS/FF	Condition	$F_{(1,\ 14)} = 6.67,\ p < 0.05$
	... × AP × LAT	n.s.	n.s.	n.s.		... × AP	n.s.
(iii) Immediate retrieval effect						... × LAT	n.s.
						... × AP × LAT	n.s.
RF/FF	Condition	n.s.	$F_{(1,\ 14)} = 6.74,\ p < 0.05$	n.s.	RR/FF	Condition	$F_{(1,\ 14)} = 9.11,\ p < 0.01$
	... × AP	n.s.	n.s.	$F_{(1.31,\ 18.27)} = 5.95,\ p < 0.05$		... × AP	$F_{(1.36,\ 19.09)} = 5.27,\ p < 0.05$
	... × LAT	n.s.	n.s.	n.s.		... × LAT	$F_{(1.31,\ 18.38)} = 4.19,\ p < 0.05$
	... × AP × LAT	n.s.	n.s.	n.s.		... × AP × LAT	$F_{(4,\ 56)} = 3.69,\ p < 0.01$

Degrees of freedom, F- and p- values are listed only for significant results ($p < 0.05$). Anterior-posterior (AP), laterality (LAT). SR, studied remembered; SF, studied forgotten; RR, remembered; RF, later forgotten; FF, immediately forgotten. Non-significant is abbreviated as n.s. Shading indicates significant outcomes.

Comparison of Restudy and Testing Condition

All restudied items (RS) vs. one tested condition (RR or RF or FF)

As reported in **Table 2B**, in this set of contrasts we explored whether and how mnemonic processing in the testing condition is reflected in the LPN, a late onsetting ERP component elicited by retrieval cues when memory contents are searched and retrieved. We first contrasted the LPN in the study condition (RS; collapsed across later forgotten [SF] and later remembered [SR] trials) separately with the three testing conditions RR, RF, and FF using ANOVAs with factors testing/restudy condition × 3 AP × 3 Laterality in the 700–1000 ms time window. For the RS vs. RR contrast there was a testing/restudy × AP interaction. Follow-up ANOVAs were performed for each level of the AP factor. While no effects were obtained at the frontal and central recordings, for the parietal recordings there was a testing/restudy by LAT interaction [$F_{(2,\ 28)} = 5.72,\ p < 0.01$]. Although this interaction is difficult to interpret, it most likely reflects a tendency for more negative going waveforms in the RR condition at right parietal recordings. In the RS/RF contrast, there were no effects involving the testing/restudy condition. Rather, the RS/FF contrast revealed a main effect of testing/restudy condition which reflects the broadly distributed LPN in the FF as compared to the RS condition.

In a final contrast, we explored whether the LPN within the testing conditions is modulated by the ease with which information can be recovered by contrasting tested items which were not retrieved at practice or Day 2 (FF) with those that were retrieved at practice and at Day 2 (RR). This analysis revealed a main effect of testing/restudy condition, interactions between the condition factor and the two other factors, AP and LAT, as well as a three-way interaction. Tested separately for each of the Laterality by AP combinations, a larger LPN for the FF than the RR condition was obtained at all nine electrode sites. *Post-hoc* analyses estimating the effect size using Cohen's *d*-values revealed that the LPN is most pronounced at left middle-posterior C3 and P3 electrode sites ($d > 0.9$) and also middle-right central Cz and C4 ($d > 0.8$) electrodes.

Taken together the LPN analyses revealed a topographically widespread (RS vs. FF contrast) and a left to midline centro-parietally accentuated LPN (RR vs. FF contrast). The LPN was generally larger in the testing condition that in the restudy condition, in line with the assumption that retrieval processes and evaluation of retrieved information took place to a greater extent in the former condition. Notably, the largest LPN difference was obtained when the restudy condition was contrasted with the testing condition (FF) for which the presumed demands on evaluative processing were largest, because these items were not recallable on either Days 1 or 2. For this latter testing condition the LPN was also larger than in the testing condition, in which items were readily assessable at Day 1 and Day 2 (RR) presumably resulting in low evaluation demands.

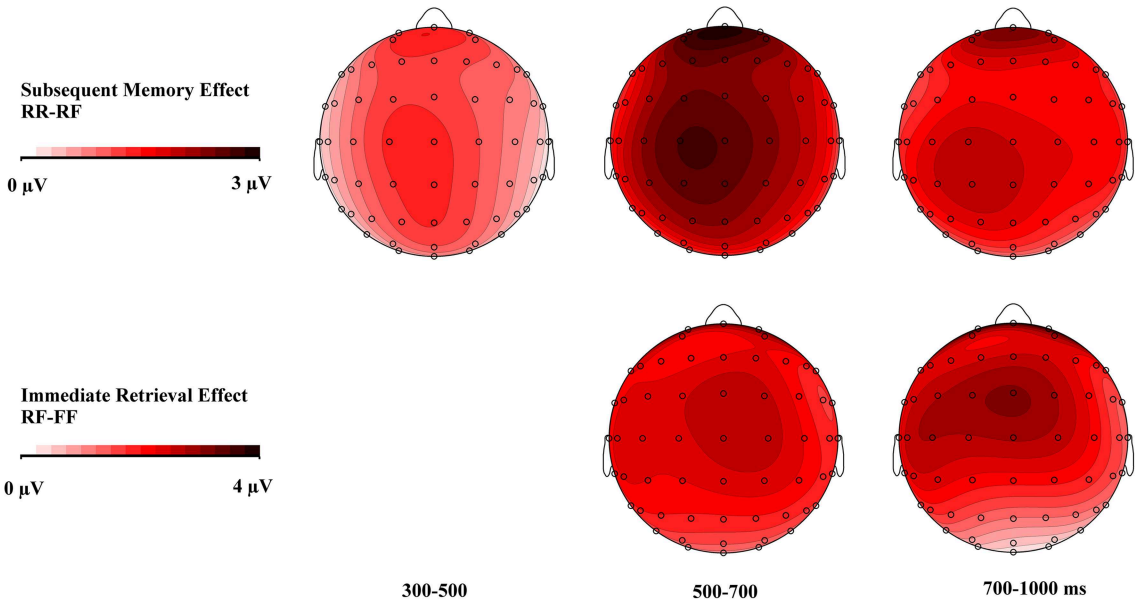


FIGURE 4 | Topographical maps showing the scalp distributions of the subsequent memory effect (RR-RF) and the immediate retrieval effect (RF-FF). The subsequent memory effect started at an earlier time window (300–500 ms). Both effects show similar scalp topography in the 500–700 ms time window. The voltage scale is from 0 to 3 μV for the subsequent memory condition and from 0 to 4 μV for the immediate retrieval condition.

Discussion

Many studies have demonstrated that testing during learning enhances later memory performance. The episodic context account is one model of the underlying mechanisms thought to drive the testing effect (Lehman et al., 2014). The core concept of this account is that retrieval practice encourages a retrieval process which leads learners to recollect the episode during learning; consequently re-instantiating the episodic context, enhancing associative processing during testing and improving retention in the final recall test.

The current ERP study provides support for the retrieval account of the testing effect. On the behavioral level, the forgetting rate from Day 1 to Day 2 was lower for pairs that were tested on Day 1 than for restudied materials. We now turn to the analyses of the ERP data to explore the neural underpinnings of this effect.

Restudy

Although SMEs were expected in both the restudy and testing condition, no such effect was observed in the restudy condition. We speculate that this is likely to be due to the inclusion of three learning blocks prior to the restudy condition in Phase 2 of the current design. The processes which predict later memory performance for the restudied items and which are typically seen in ERP SME contrasts (i.e., Paller and Wagner, 2002) could have occurred during any of the preceding learning blocks, rendering them unobservable during Phase 2. This jittering of the point at which encoding occurred is likely to have diluted the SME in the restudy condition. An alternative, yet related account for the absent SME effect arises from considering studies which demonstrated a reversed SME in ERPs to non-words as compared to the SME to real words (e.g., Otten et al., 2007) or from studies which did not obtain SME in conditions in which items were not semantically processed (Mecklinger and Müller, 1996). The potential implications of this therefore are that seeing a restudied word pair for the fourth time reduces the likelihood of engaging in semantic processing or explicit encoding processes that are usually observed for real words seen in standard SME paradigms. It is not possible to consider the likelihoods of specific mechanisms on the basis of these data alone. However, the absence of an SME in the restudy condition alongside the robust SME in the testing condition strongly supports the core assumption of the episodic context account that testing conditions uniquely elicit mnemonic processes, which confer benefits for later recall. In the following, it is argued that the current data strongly indicate that these processes include recollection.

Testing

The first contrast between items in the testing condition revealed ERPs to later-remembered items (RR) that were more positive-going than ERPs to items that were later-forgotten (RF). This finding is in line with our prediction despite the fact that this effect was widely distributed across the scalp at all time windows from 300 up to 1000 ms after stimulus onset, which has an earlier onset than the predicted time window in which the neural correlates of recollection were often observed (Paller and Wagner, 2002).

The contrast between RF and FF was presumed to reflect immediate-retrieval processes. This contrast was significant in

the time window from 500 to 700 ms in which the parietal old/new effect, the ERP correlate of recollection is usually found (Rugg and Curran, 2007). Although the ERP correlate of recollection has been reported to focus principally at parietal recording sites (Vilberg and Rugg, 2008), we find only a main effect of Memory condition in this specific time window. Previous studies have also found the parietal old/new effect to be larger and more widely distributed in free recall task than in recognition task (Paller et al., 1988). In addition, it is also conceivable that cues in a foreign language evoke processes additional to the recollection processes and this may have rendered the effect more widely distributed across the scalp.

Notably, when contrasting the SME and immediate retrieval effect between 500 and 700 ms, we find that the effects do not differ in scalp topography even when a highly sensitive measure for topographical differences including 58 scalp electrodes was used. Although null findings require particular caution in EEG, these data are in line with the engagement of qualitatively similar neural circuitry associated with recollective processing in the two cases. The current findings support the episodic context account, which assumes that the testing effect is likely to be driven by an engagement of recollection at testing. Recollection can bind multiple aspects to represent an episode and recollective processing during testing may have strengthened the previously formed word-word associations or may have produced novel associations that facilitated retrieval on Day 2. By this the current data provide electrophysiological support for the retrieval account of the testing effect and complement brain imaging studies exploring the testing effect using the SME paradigm (van den Broek et al., 2013; Wing et al., 2013). A second but not mutually exclusive possibility is that the amplitude of ERPs for tested items in the 500–700 ms time window was modulated by memory strength. Visual inspection of this effect reveals a gradient of increasing amplitude among the three testing conditions (RR > RF > FF) in this time window (**Figure 3B**). To explore this possibility, we conducted an additional *post-hoc* analysis of the amplitude differences across the three testing conditions in this time window. An ANOVA with three testing conditions and AP and Laterality as factors revealed a main effect of testing condition, $F_{(1.43,\ 19.99)} = 13.18$, $p < 0.01$. The ERPs become increasingly positive the better an item was remembered, with largest values for word pairs remembered on Day 2 (RR) intermediate values for pairs remembered on Day 1 only (RF) and smallest values for words which were already forgotten at practice (FF). This effect is consistent with the view that items with high memory strength are better recollected; meaning that more information is in an accessible state and more likely to be remembered at both days.

LPN is Associated with Post-Retrieval Memory Search

In the late (700–1000 ms) time interval, an LPN was obtained which was generally larger in the testing than in the restudy condition. Notably, these LPN differences between testing and restudy were only obtained when the restudy condition was contrasted with the testing condition (FF) that imposed the highest demands on post-retrieval evaluative processing. In this latter testing condition the LPN was also larger than in the testing condition in which items were readily assessable resulting in low evaluation demands (RR). This pattern of results is consistent with the view that the LPN is most pronounced in situations with a high need for continuous evaluation of memory bound information. Notably the current results are also consistent with a second account of the LPN, namely that it is modulated by the specificity with which memory is searched. In one illustrative source memory study (Leynes and Kakadia, 2013) participants were required to discriminate either between performed and watched actions or between performed and interrupted actions. There was a large LPN when performed and interrupted actions had to be discriminated, i.e., a condition with a high amount of overlapping features between both sources in which as a consequence only a few features were diagnostic for the source decision. The LPN in the latter study was much smaller when performed and watched actions had to be discriminated and the two sources could be discriminated on a simple 1st vs. 3rd person perspective. In this framework, it is conceivable that a cued recall test such as the one used in the current testing condition imposes high demands for a highly specific memory search, as it requires one to discriminate between phonologically and semantically overlapping words in order to identify the item originally paired with the cue word. The highly overlapping lexical features of the German-target words may have lowered memory strength and may have given rise to extended retrieval processing as reflected in the LPN, particularly in situations in which retrieval processing was unsuccessful.

Caveats

Although a robust benefit of testing was demonstrated when the amounts of forgetting from Day 1 to Day 2 were compared between testing and restudy conditions, only a marginally significant difference between testing and restudy on Day 2 was observed. This could arise from a number of aspects of the current design. Unlike studies which controlled for learning success before retrieval practice took place (Karpicke and Roediger, 2008; van den Broek et al., 2013), in the current study, participants learned all word pairs three times before the critical manipulation was introduced. Given the large number of test items required to provide sufficient ERP trials, the relatively high task difficulty may have meant some items were not encoded sufficiently within the initial three learning blocks. For those items not learned during Phase 1, once they were assigned to the testing condition, there was a low-likelihood that the items would be recovered. In contrast, the unlearned items from Phase 1 would receive a fourth learning opportunity once they were assigned into the restudy condition (Bahrick and Hall, 1991; Jang et al., 2012). This restriction of the experimental design conveys a disadvantage for tested items over restudied items on Day 1 (Toppino and Cohen, 2009), because the latter are shown again during Phase 2.

Another aspect of the testing paradigm sounds a note of caution when interpreting the ERP testing effects as SME. We took the increasing positivity from RF to RR as a correlate of processes that support later retrieval and therefore as a SME. However, it is possible that any effect which influences ERPs

during memory retrieval can be mistaken for encoding effects caused by testing itself. It is principally not possible to determine whether these ERP effects reflect more general differences in memory strength as assumed by the memory strength account or are consequences of different memory strengths caused by former encoding as assumed by the retrieval account. For example, there could have been general a priori differences in memory strength between RR and FF word pairs rendering the former easier to retrieve than the latter. If this was the case, the ERP effects would reflect an item selection bias. Due to the high number of word pairs that we used in the present study we do not believe that a selection bias was at work but this issue should be more directly addressed in further studies.

In summary, the current study provides a direct link between the neural correlates of the SME and of immediate retrieval at the time point when testing occurs in comparison to restudy condition. Our findings support the episodic context account that testing engages recollection and that enhanced recollective processes improve retention in a later cued recall task. A second possible explanation is that the higher memory strength is, the higher is recallability on a later recall task and this retrieval practice further enhances later memory on a delayed test. In addition, we also show that at a late stage of retrieval processing the LPN reflects a highly specific memory search presumably imposed by the overlapping features of the to-be-discriminated words during cued recall.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnbeh.2015.00248

References

Baayen, R. H., Piepenbrock, R., and Gulikers, L. (1995). *The CELEX Lexical Database*. Pennsylvania, PA: Linguistic Data Consortium, University of Pennsylvania.

Bader, R., Mecklinger, A., Hoppstädter, M., and Meyer, P. (2010). Recognition memory for one-trial-unitized word pairs: evidence from event-related potentials. *Neuroimage* 50, 772–781. doi: 10.1016/j.neuroimage.2009.12.100

Bahrick, H., and Hall, L. (1991). Preventive and corrective maintenance of access to knowledge. *Appl. Cogn. Psychol.* 5, 1–18. doi: 10.1002/acp.2350050102

Bjork, R. A. (1975). "Retrieval as a memory modifier: an interpretation of negative recency and related phenomena," in *Information Processing and Cognition: The Loyola Symposium,* ed R. Solso (Hillsdale, NJ: Lawrence Erlbaum), 123–144.

Butler, A. C., and Roediger, H. L. (2007). Testing improves long-term retention in a simulated classroom setting. *Eur. J. Cogn. Psychol.* 19, 514–527. doi: 10.1080/09541440701326097

Cabeza, R., Ciaramelli, E., Olson, I. R., and Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nat. Rev. Neurosci.* 9, 613–625. doi: 10.1038/nrn2459

Carpenter, S. K. (2009). Cue strength as a moderator of the testing effect: the benefits of elaborative retrieval. *J. Exp. Psychol. Learn. Mem. Cogn.* 35, 1563–1569. doi: 10.1037/a0017021

Carpenter, S. K. (2011). Semantic information activated during retrieval contributes to later retention: support for the mediator effectiveness hypothesis of the testing effect. *J. Exp. Psychol. Learn. Mem. Cogn.* 37, 1547–1552. doi: 10.1037/a0024140

Carpenter, S. K., and DeLosh, E. L. (2006). Impoverished cue support enhances subsequent retention: support for the elaborative retrieval explanation of the testing effect. *Mem. Cogn.* 34, 268–276. doi: 10.3758/BF03193405

Davachi, L., Maril, A., and Wagner, A. (2001). When keeping in mind supports later bringing to mind: neural markers of phonological rehearsal predict subsequent remembering. *J. Cogn. Neurosci.* 13, 1059–1070. doi: 10.1162/089892901753294356

Diana, R. A., Yonelinas, A. P., and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn. Sci.* 11, 379–386. doi: 10.1016/j.tics.2007.08.001

Eriksson, J., Kalpouzos, G., and Nyberg, L. (2011). Rewiring the brain with repeated retrieval: a parametric fMRI study of the testing effect. *Neurosci. Lett.* 505, 36–40. doi: 10.1016/j.neulet.2011.08.061

Friedman, D., and Johnson, R. (2000). Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microsc. Res. Tech.* 51, 6–28. doi: 10.1002/1097-0029(20001001)51:1<6::AID-JEMT2>3.0.CO;2-R

Halsband, T. M., Ferdinand, N. K., Bridger, E. K., and Mecklinger, A. (2012). Monetary rewards influence retrieval orientations. *Cogn. Affect. Behav. Neurosci.* 12, 430–445. doi: 10.3758/s13415-012-0093-y

Hutchinson, J. B., Uncapher, M. R., Weiner, K. S., Bressler, D. W., Silver, M. A., Preston, A. R., et al. (2014). Functional heterogeneity in posterior parietal cortex across attention and episodic memory retrieval. *Cereb. Cortex* 24, 49–66. doi: 10.1093/cercor/bhs278

Jacoby, L. L. (1991). A process dissociation framework: separating automatic from intentional uses of memory. *J. Mem. Lang.* 30, 513–541. doi: 10.1016/0749-596X(91)90025-F

Jacoby, L. L. (1998). Invariance in automatic influences of memory: toward a user's guide for the process-dissociation procedure. *J. Exp. Psychol. Learn. Mem. Cogn.* 24, 3–26. doi: 10.1037/0278-7393.24.1.3

Jang, Y., Wixted, J. T., Pecher, D., Zeelenberg, R., and Huber, D. E. (2012). Decomposing the interaction between retention interval and study / test practice: the role of retrievability. *Q. J. Exp. Psychol. A* 65, 962–975. doi: 10.1080/17470218.2011.638079

Johansson, M., and Mecklinger, A. (2003). The late posterior negativity in ERP studies of episodic memory: action monitoring and retrieval of attribute conjunctions. *Biol. Psychol.* 64, 91–117. doi: 10.1016/S0301-0511(03)00104-2

Karpicke, J. D., and Roediger, H. L. (2008). The critical importance of retrieval for learning. *Science* 319, 966–968. doi: 10.1126/science.1152408

Karpicke, J., Lehman, M., and Aue, W. R. (2014). "Retrieval-based learning: An episodic context account," in *Psychology of Learning and Motivation,* Vol. 61, ed B. H. Ross (San Diego, CA: Elsevier Inc.), 237–284.

Lehman, M., Smith, M. A., and Karpicke, J. D. (2014). Toward an episodic context account of retrieval-based learning: dissociating retrieval practice and elaboration. *J. Exp. Psychol. Learn. Mem. Cogn.* 40, 1–8. doi: 10.1037/xlm0000012

Leynes, P. A., and Kakadia, B. (2013). Variations in retrieval monitoring during action memory judgments: evidence from event-related potentials (ERPs). *Int. J. Psychophysiol.* 87, 189–199. doi: 10.1016/j.ijpsycho.2013.01.004

Makeig, S., Debener, S., Onton, J., and Delorme, A. (2004). Mining event-related brain dynamics. *Trends Cogn. Sci.* 8, 204–210. doi: 10.1016/j.tics.2004.03.008

McCarthy, G., and Wood, C. C. (1985). Scalp distributions of event-related potentials: an ambiguity associated with analysis of variance models.

Electroencephalogr. Clin. Neurophysiol. Evoked Potentials Sec. 62, 203–208. doi: 10.1016/0168-5597(85)90015-2

McDaniel, M. A., and Fisher, R. P. (1991). Tests and test feedback as learning sources. *Contemp. Educ. Psychol.* 16, 192–201. doi: 10.1016/0361-476X(91)90037-L

McDaniel, M. A., Kowitz, M. D., and Dunay, P. K. (1989). Altering memory through recall: the effects of cue-guided retrieval processing. *Mem. Cogn.* 17, 423–434. doi: 10.3758/BF03202614

McDaniel, M., and Masson, M. (1985). Altering memory representations through retrieval. *J. Exp. Psychol. Learn. Mem. Cogn.* 11, 371–385. doi: 10.1037/0278-7393.11.2.371

Mecklinger, A. (2000). Interfacing mind and brain: a neurocognitive model of recognition memory. *Psychophysiology* 37, 565–582. doi: 10.1111/1469-8986.3750565

Mecklinger, A., and Müller, N. (1996). Dissociations in the processing of "what" and "where" information in working memory: an event-related potential analysis. *J. Cogn. Neurosci.* 8, 453–473. doi: 10.1162/jocn.1996.8.5.453

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Otten, L. J., Sveen, J., and Quayle, A. H. (2007). Distinct patterns of neural activity during memory formation of nonwords versus words. *J. Cogn. Neurosci.* 19, 1776–1789. doi: 10.1162/jocn.2007.19.11.1776

Paller, K. A., McCarthy, G., and Wood, C. C. (1988). ERPs predictive of subsequent recall and recognition performance. *Biol. Psychol.* 26, 269–276. doi: 10.1016/0301-0511(88)90023-3

Paller, K. A., and Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn. Sci.* 6, 93–102. doi: 10.1016/S1364-6613(00)01845-3

Pyc, M. A., and Rawson, K. A. (2009). Testing the retrieval effort hypothesis: does greater difficulty correctly recalling information lead to higher levels of memory? *J. Mem. Lang.* 60, 437–447. doi: 10.1016/j.jml.2009.01.004

Roediger, H. III., and Karpicke, J. (2006). The power of testing memory: basic research and implications for educational practice. *Perspect. Psychol. Sci.* 1, 181–210. doi: 10.1111/j.1745-6916.2006.00012.x

Roediger, H. L. III., and Butler, A. C. (2011). The critical role of retrieval practice in long-term retention. *Trends Cogn. Sci.* 15, 20–27. doi: 10.1016/j.tics.2010.09.003

Rosburg, T., Johansson, M., Weigl, M., and Mecklinger, A. (2015). How does testing affect retrieval-related processes? An event-related potential (ERP) study on the short-term effects of repeated retrieval. *Cogn. Affect. Behav. Neurosci.* 15, 195–210. doi: 10.3758/s13415-014-0310-y

Rosburg, T., Mecklinger, A., and Johansson, M. (2011). Electrophysiological correlates of retrieval orientation in reality monitoring. *Neuroimage* 54, 3076–3084. doi: 10.1016/j.neuroimage.2010.10.068

Rugg, M. D., and Curran, T. (2007). Event-related potentials and recognition memory. *Trends Cogn. Sci.* 11, 251–257. doi: 10.1016/j.tics.2007.04.004

Shapiro, S. S., and Wilk, M. B. (1965). An analysis of variance test for normality (complete samples). *Biometrika* 52, 591–611. doi: 10.1093/biomet/52.3-4.591

Skavhaug, I. M., Wilding, E. L., and Donaldson, D. I. (2010). Judgments of learning do not reduce to memory encoding operations: event-related potential evidence for distinct metacognitive processes. *Brain Res.* 1318, 87–95. doi: 10.1016/j.brainres.2009.11.047

Toppino, T. C., and Cohen, M. S. (2009). The testing effect and the retention interval: questions and answers. *Exp. Psychol.* 56, 252–257. doi: 10.1027/1618-3169.56.4.252

van den Broek, G. S. E., Takashima, A., Segers, E., Fernández, G., and Verhoeven, L. (2013). Neural correlates of testing effects in vocabulary learning. *Neuroimage* 78, 94–102. doi: 10.1016/j.neuroimage.2013.03.071

Vilberg, K. L., Moosavi, R. F., and Rugg, M. D. (2006). The relationship between electrophysiological correlates of recollection and amount of information retrieved. *Brain Res.* 1122, 161–170. doi: 10.1016/j.brainres.2006.09.023

Vilberg, K. L., and Rugg, M. D. (2008). Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. *Neuropsychologia* 46, 1787–1799. doi: 10.1016/j.neuropsychologia.2008.01.004

Wing, E. A., Marsh, E. J., and Cabeza, R. (2013). Neural correlates of retrieval-based memory enhancement: an fMRI study of the testing effect. *Neuropsychologia* 51, 2360–2370. doi: 10.1016/j.neuropsychologia.2013.04.004

Yonelinas, A. P., Aly, M., Wang, W. C., and Koen, J. D. (2010). Recollection and familiarity: examining controversial assumptions and new directions. *Hippocampus* 20, 1178–1194. doi: 10.1002/hipo.20864

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