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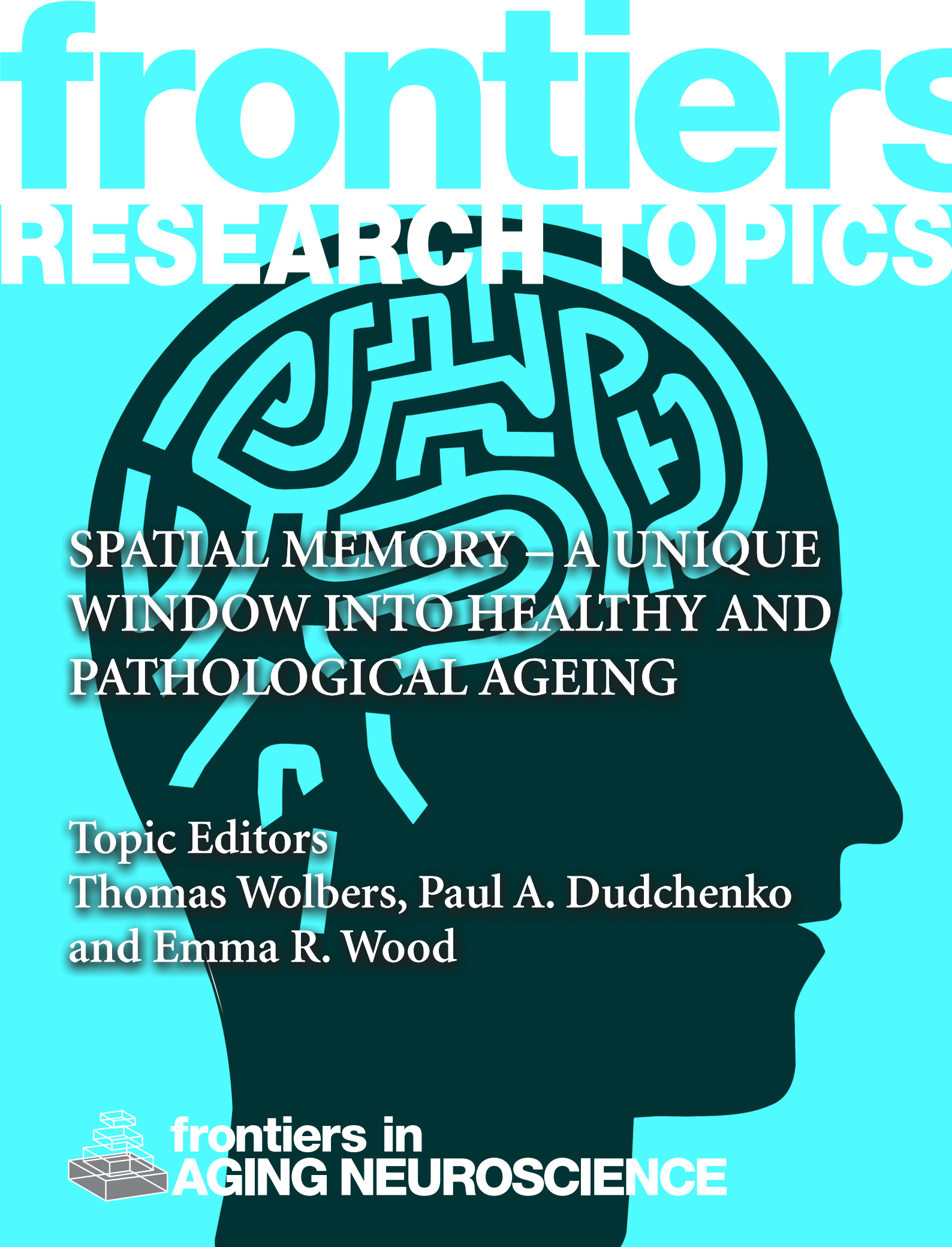

SPATIAL MEMORY – A UNIQUE WINDOW INTO HEALTHY AND PATHOLOGICAL AGEING

Topic Editors
Thomas Wolbers, Paul A. Dudchenko and Emma R. Wood

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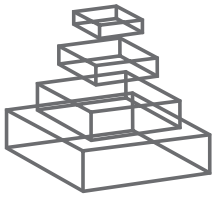

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ISSN 1664-8714
ISBN 978-2-88919-386-8
DOI 10.3389/978-2-88919-386-8

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SPATIAL MEMORY – A UNIQUE WINDOW INTO HEALTHY AND PATHOLOGICAL AGEING

Topic Editors:
Thomas Wolbers, German Center for Neurodegenerative Diseases, Germany
Paul A. Dudchenko, University of Stirling, United Kingdom
Emma R. Wood, University of Edinburgh, United Kingdom

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AGING NEUROSCIENCE

EDITORIAL
published: 07 March 2014
doi: 10.3389/fnagi.2014.00035

Spatial memory—a unique window into healthy and pathological aging

Thomas Wolbers[1]*, Paul A. Dudchenko[2] and Emma R. Wood[3]

[1] *Aging and Cognition Research Group, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany*
[2] *School of Natural Sciences, University of Stirling, Stirling, UK*
[3] *School of Biomedical Sciences, University of Edinburgh, Edinburgh, UK*
**Correspondence: thomas.wolbers@dzne.de*

Edited by:
Rodrigo O. Kuljiš, The University of Texas Medical Branch, USA

Keywords: spatial navigation, aging, dementia, neuroscience, animal models, humans

The world's population is aging at an unprecedented rate, because the number of people aged over 60 will rise from 784 million in 2011 to 2 billion by 2050. Such a dramatic increase has made age-related cognitive decline and Alzheimer's disease (AD) a pressing social and health concern. Work described in this volume considers scientific efforts to understand the neural mechanisms of age-related changes in spatial navigation, both in humans and non-human animal models. A central theme in these papers is that damage to structures of the medial temporal lobe, including the hippocampus, contributes to the difficulties in spatial memory found in aging and AD.

Tanila (2012) describes the use of the Morris Water Maze (MWM) task as a tool for demonstrating memory impairments in mouse models of AD. Tanila (2012) points out important challenges in working with mice compared to rats—the former are prone to hypothermia, and exhibit strain differences in learning capacity. Strikingly, an impairment on the swim task is seen in all established models of AD in mice, though its relationship to the onset of amyloid plaque deposition or tau aggregation varies.

In the MWM, Yau and Seckl (2012) note that older rats with impaired performance have higher corticosterone levels than those who are unimpaired. Higher corticosterone levels shift the balance between mineralcorticoid- and glucocorticoid-receptor activation, and are associated with decreases in long-term potentiation and memory. Yau and Seckl (2012) review findings which show that reduction of an enzyme that increases glucocorticoids results in improved spatial memory in aged rodents.

Holden and Gilbert (2012) review studies which show that pattern separation abilities are impaired in older humans, monkeys, and rodents. Such a capacity likely relies on the hippocampus, and in particular the dentate gyrus/CA3 cell regions. They hypothesize that impaired pattern separation may result in impaired episodic memory in aging.

Penner and Mizumori (2012) also relate the pattern separation function of the hippocampus in terms of the recognition of contexts. Their proposal is that the hippocampus produces an error signal when a context is unexpected, and this ultimately drives dopaminergic neurons in the ventral tegmental area. Aging affects this circuit by altering hippocampal representations of context, mesolimbic-ventral striatum interactions, and the dopaminergic system.

Turning to humans, Adamo et al. (2012) investigated how aging affects path integration, a key navigational process. Both task complexity and the sources of information available to participants (i.e., visual vs. vestibular) had a substantial impact on the results. These findings have important methodological implications, because studies on spatial navigation are often confined to one sensory modality and do not systematically manipulate task complexity.

Several studies demonstrate deficits in allocentric processing in healthy older adults. Rosenbaum et al. (2012) showed that memory for the layout of long familiar Toronto landmarks did not differ dramatically between young and older participants, but the latter made many more errors in learning a new route in a hospital. These results support a model where episodic-like representations of spatial information (hippocampus dependent) give rise to more schematic (less detailed, but hippocampus independent) representations with repeated experience.

Using virtual environment (VE) technology, Yamamoto and DeGirolamo (2012) found that older participants had difficulties reconstructing the layouts of landmarks encountered in a virtual city. Interestingly, performance was not impaired when they experienced the environments from a bird's eye perspective. These results suggest that spatial learning through exploratory navigation may be particularly vulnerable to adverse effects of aging, whereas elderly adults may be able to maintain their map reading skills relatively well.

Wiener et al. (2012) had participants learn a route through a VE that contained multiple intersections. Compared to young controls, older adults had greater problems during route retracing than during route repetition. While route repetition can be solved with egocentric response or route strategies, successfully retracing a route requires allocentric processing. These age-related deficits in route retracing are discussed in the context of a potential shift from allocentric to egocentric navigation strategies as a consequence of age-related hippocampal degeneration.

A bias toward egocentric response strategies with increasing age was also observed by Bohbot et al. (2012). A virtual 8-arm radial maze served to assess spontaneous navigation strategies, i.e., hippocampal-dependent spatial strategies vs. caudate nucleus-dependent response strategies. Results showed that from childhood to old age, the spontaneous use of egocentric response strategies increased substantially. In a related study, Konishi and Bohbot (2013) showed that spontaneous spatial memory strategies positively correlated with gray matter density in the hippocampus of older participants. The combined results from both

studies indicate that people who prefer to use spatial memory strategies in their everyday lives may have increased gray matter in the hippocampus and enhance the probability of healthy aging.

Beyond the hippocampus, aging also affects the integrity of a larger network of brain structures, including prefrontal cortex. Harris et al. (2012) found that older humans were impaired at switching from a route strategy to a place strategy on a virtual plus maze task. Interestingly, this did not reflect a general difficulty in switching between spatial strategies, as the switch from a place strategy to a route strategy was not impaired. This may imply that interactions between the prefrontal cortex and the hippocampus are affected with advanced age.

Finally, Pengas et al. (2012) demonstrate that spatial navigation impairments in AD relate to damage across a network, which offers complimentary lesion evidence to studies in healthy volunteers for the neural basis of topographical memory. Critically, the results emphasize that structures beyond the medial temporal lobe contribute to memory impairment in AD, which argues against common models in which memory impairment in AD is taken as a synonym for hippocampal degeneration.

The book concludes with a review of human aging and spatial navigation tasks by Gazova et al. (2012). They suggest that such navigation tasks may be a useful tool for identifying individuals who will go on to develop AD. Given the growing number of studies indicating that damage to the medial temporal lobe (including the hippocampus) is associated with wayfinding difficulties, Gazova et al. (2012) argue that the use of such spatial tasks may help to identify AD early in its course.

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Received: 08 November 2013; accepted: 19 February 2014; published online: 07 March 2014.

Citation: Wolbers T, Dudchenko PA and Wood ER (2014) Spatial memory—a unique window into healthy and pathological aging. Front. Aging Neurosci. ***6****:35. doi: 10.3389/fnagi.2014.00035*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 20 February 2013
doi: 10.3389/fnagi.2013.00001

Spatial navigational strategies correlate with gray matter in the hippocampus of healthy older adults tested in a virtual maze

Kyoko Konishi* and *Véronique D. Bohbot*

Department of Psychiatry, Douglas Institute, McGill University, Verdun, QC, Canada

Edited by:
Thomas Wolbers, German Center for Neurodegenerative Diseases, Germany

Reviewed by:
Diego Ruano, University of Sevilla, Spain
Barbara Shukitt-Hale, United States Department of Agriculture, USA

***Correspondence:**
Véronique D. Bohbot, Department of Psychiatry, Faculty of Medicine, McGill University, Douglas Mental Health University Institute, FBC Building, 6875 boul. LaSalle, Verdun, QC H4H 1R3, Canada.
e-mail: veronique.bohbot@mcgill.ca

Healthy young adults use different strategies when navigating in a virtual maze. Spatial strategies involve using environmental landmarks while response strategies involve executing a series of movements from specific stimuli. Neuroimaging studies previously confirmed that people who use spatial strategies show increased activity and gray matter in the hippocampus, while those who use response strategies show increased activity and gray matter in caudate nucleus (Iaria et al., 2003; Bohbot et al., 2007). A growing number of studies report that cognitive decline that occurs with normal aging is correlated with a decrease in volume of the hippocampus. Here, we used voxel-based morphometry (VBM) to examine whether spatial strategies in aging are correlated with greater gray matter in the hippocampus, as found in our previous study with healthy young participants. Forty-five healthy older adults were tested on a virtual navigation task that allows spatial and response strategies. All participants learn the task to criterion after which a special "probe" trial that assesses spatial and response strategies is given. Results show that spontaneous spatial memory strategies, and not performance on the navigation task, positively correlate with gray matter in the hippocampus. Since numerous studies have shown that a decrease in the volume of the hippocampus correlates with cognitive deficits during normal aging and increases the risks of ensuing dementia, the current results suggest that older people who use their spatial memory strategies in their everyday lives may have increased gray matter in the hippocampus and enhance their probability of healthy and successful aging.

Keywords: aging, radial maze, spatial memory, hippocampus, navigation

INTRODUCTION

Multiple studies have demonstrated that age impairs spatial memory in both humans and non-human species (Barnes et al., 1980; Marighetto et al., 1999; Driscoll et al., 2003; Wood and Dudchenko, 2003; Moffat et al., 2006; Antonova et al., 2009; Iaria et al., 2009). Older adults report to having more navigation problems with increasing age and admit to avoiding traveling unfamiliar routes (Burns, 1999). Furthermore, "getting lost" behavior and impairment in spatial memory are early symptoms of cognitive impairment and Alzheimer's disease (Klein et al., 1999; deIpolyi et al., 2007; Hort et al., 2007).

When navigating in a virtual environment, studies showed that participants spontaneously use one of two navigational strategies (Packard and McGaugh, 1996; Iaria et al., 2003). Spatial memory, or the "spatial strategy," is one of two navigation strategies that can be used when going places (Packard et al., 1989; Packard and McGaugh, 1996; Iaria et al., 2003; Bohbot et al., 2007). It involves navigating within an environment by forming relationships between different landmarks in the environment and orientating oneself in relation to those landmarks. This process of forming associations between landmarks leads to the development of cognitive maps, i.e., mental representations of one's environment. Knowledge of the relationships between landmarks is characterized with flexibility, allowing, for example, one to derive a direct path to a target destination when navigating in a town (O'Keefe and Nadel, 1978). The spatial strategy is subserved by the hippocampus (O'Keefe and Nadel, 1978; Morris et al., 1982; Abrahams et al., 1997; Bohbot et al., 1998). In contrast, the "response strategy" involves learning a series of stimulus-response associations such as a pattern of left and right turns from a given starting position. This strategy is inflexible in the sense that it does not allow deriving a direct path to a target location (O'Keefe and Nadel, 1978). The response strategy relies on the striatum, which includes the caudate nucleus in humans (Packard et al., 1989; Packard and Knowlton, 2002; White and McDonald, 2002).

In a previous study (Bohbot et al., 2007), we tested healthy young adult participants on a virtual navigation task that can be solved using either a spatial or response strategy. We found that spatial learning positively correlated with gray matter in the hippocampus, while response learning positively correlated with caudate nucleus gray matter. Furthermore, an inverse relationship was found between gray matter in the hippocampus and caudate nucleus. In other words, those who had more gray matter in the hippocampus had less gray matter in the caudate nucleus and vice versa. In addition, participants' peak hippocampal values correlated with gray matter in a network of regions anatomically

connected to the hippocampus, such as the perirhinal, entorhinal and parahippocampal cortices, the orbitofrontal cortex, and the amygdala. There was also a significant correlation with gray matter in the contralateral hippocampus.

Several studies have examined the neural correlates of spatial memory in older adults. Using manual segmentation, Chen et al. (2010) and Head and Isom (2010) found that performance on a virtual spatial memory task correlated with total volume of the hippocampus. Head and Isom (2010) additionally found a positive correlation between caudate nucleus volume and performance on a virtual route learning task, a task known to utilize response strategies.

In the present study, we investigated whether performance on our navigation task that distinguishes between spontaneous spatial and response strategies correlated with gray matter in the hippocampus and caudate nucleus in healthy older adults, using the technique of voxel-based morphometry (VBM). We hypothesized that older adults who use spatial strategies would have more gray matter in the hippocampus while those who use response strategies would have more gray matter in the caudate nucleus. Furthermore, similar to results reported in Bohbot et al. (2007), we hypothesized that those with more gray matter in the hippocampus would have more gray matter in the associated network of neuroanatomically connected regions. Since gray matter in the hippocampus is associated with healthy cognition in aging, the variability in navigational strategies could potentially help distinguish a healthy older adult from an older adult at risk for cognitive deficits. Identifying such risk factors can have a profound impact on the well-being of older adults. This is especially relevant considering the current international demographics showing a growing aging population. By the year 2050, 16% of the world population will be over the age of 65. In the US, 20% of the population is expected to be over the age 65 by 2050 and in Japan, 38% of the population is expected to be over 65 by 2050. Consequently, the current paper may bring novel insights into healthy and unhealthy aging that can help define early detection methods in view of early intervention to promote healthy aging.

MATERIALS AND METHODS

PARTICIPANTS

Forty-five healthy older adults (mean age $= 64.38 \pm 4.0$; 23 women and 22 men) participated in the study. All participants were right-handed and had normal or corrected vision. All participants were screened for any history of neurological or psychiatric disorders, alcohol, or drug abuse using a pre-screening questionnaire. All participants underwent a neuropsychological assessment to control for dementia, depression, and mild cognitive impairment (**Table 1**). Informed consent was obtained from all participants in accordance with the guidelines of the local ethics committee. The study was approved by the Research Ethics Board at the Douglas Mental Health University Institute and the Montreal Neurological Institute.

Table 1 | Older adult participant demographics and test means [SEM].

PARTICIPANT CHARACTERISTICS	
N	45
Women:Men	23:22
Age (years)	64.38 ± 4.05
IQ	107.5 ± 13.12
Education (years)	15.48 ± 2.45
Handedness	Right
NEUROPSYCHOLOGICAL TEST SCORES	
MMSE	29.21 ± 0.91
MoCA	27.48 ± 1.65

BEHAVIORAL TASKS

Concurrent spatial discrimination learning task

The Concurrent Spatial Discrimination Learning Task (CSDLT) was created using the editor program of Unreal Tournament 2003 (Epic Games, Raleigh, NC). The task is situated in a radial maze surrounded by an enriched environment made up of a landscape and proximal and distal landmarks such as plants and hills (**Figure 1**). It consists of a center platform from which branch out 12 pathways. At the end of each pathway, there is a set of stairs that leads to a small pit where, in some of the arms, an object is located. The 12 arms of the maze are divided up into six adjacent pairs of arms. Within each pair of arms, one arm always contains an object while the other is always empty. During the experimental encoding phase (Stage 1), participants are repeatedly presented with the six pairs of arms in a pseudo-random order. They are asked to learn which arm contains an object within each pair of arms and to go down that arm to retrieve the object. Upon descending the stairs at the end of the pathway and entering the pit, participants are automatically brought back to the center platform and presented with the next pair of arms. The number of correct arms the participant visits within each trial is measured as choice accuracy. One trial consists of the presentation of all six pairs of arms. Participants are trained until a choice accuracy criterion of 11/12 is reached within two consecutive trials. A minimum of six trials is administered to all participants.

Upon reaching criterion, participants proceed to a test phase aimed as dissociating the strategies used during the encoding phase of the task. The test or probe phase (Stage 2), is also called the "recombined pairs" condition because, during this phase, the arms presented to the participants are rearranged into novel pairs; however, the reward contingency remains the same. In other words, during the recombined pairs condition, the objects are placed at the end of the same arms as during the encoding phase. Four pairs of recombined arms are presented twice in a pseudo-random order. Only four recombined pairs allowed for the presentation of adjacent arms with only one arm containing an object. The recombined pairs condition was designed in such a way that successful performance on this stage requires that individuals be flexible at using the information they learned during the encoding phase of the task, evidenced by the fact that they know the spatial relationship between the object and environmental landmarks (i.e., the spatial strategy). In other words, when the pairs of arms that are presented are recombined, participants who know the relationship between the target objects and landmarks are capable of discerning the target arm from the non-target arm. In contrast, people who did not show flexibility

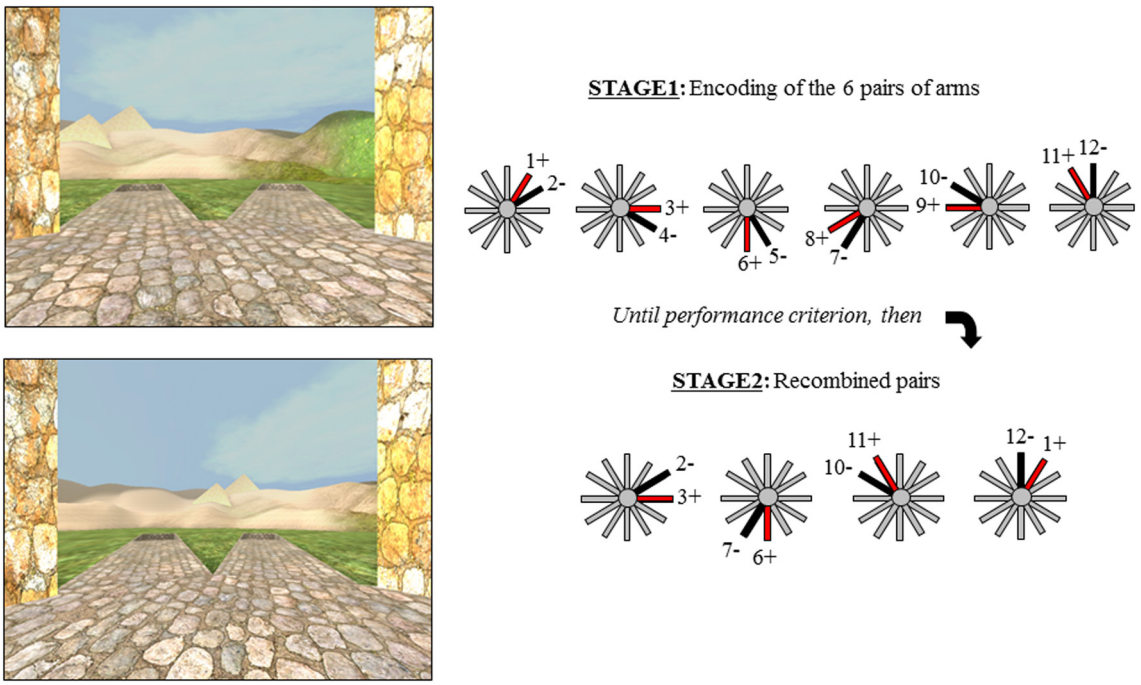

FIGURE 1 | The two stages of the virtual radial maze with a schematic representation of the behavioral paradigm. Example of a pair of arms presented during encoding (Stage 1) and a recombined pair during Stage 2.

during the recombined pairs have acquired the task by using a response strategy, i.e., "when I see the hills, take the arm to the left." In this case, since the pairs of presented arms were rearranged, "when I see the hills, take the arm to the left" in this recombined pairs stage is not the same arm as in the encoding stage. Thus, the recombined pairs stage allows us to distinguish between participants who are flexible and used a spatial strategy and those who are inflexible and used a response strategy in an objective fashion.

Rey auditory verbal learning test

The Rey Auditory Verbal Learning Test (RAVLT) is a standard neuropsychological memory test (Lezak, 1995). A list of 15 words (list A) is read for five trials and after each trial the participant is asked to verbally recall as many words as they can remember. Next, an interference trial is provided whereby a different list of 15 words (list B) is read to the participant and again the participant is asked to recall as many words as they can remember. Following this interference trial, the participant is asked to recall as many words as they can from list A. Finally, after a 30-min delay, the participant is again asked to remember as many words as they can from list A. Performance was assessed with the number of words recalled after interference (AI) and after the 30-min delay (delayed recall).

Rey-osterrieth complex figure

In the Rey-Osterrieth Complex Figure task (RO) (Osterrieth, 1944), participants are asked to copy a complex figure in as much detail as possible. After a 30-min delay, participants are asked to redraw the complex figure from memory in as much detail as they can.

MAGNETIC RESONANCE IMAGING (MRI) SCANNING PROTOCOL

Structural MRI scans were obtained at the Montreal Neurological Institute with a 1.5T Siemens Sonata MRI scanner. Participants were comfortably placed in the scanner with their heads immobilized using an air cushion. An anatomical scan of ∼15 min was taken for each participant. A 3D gradient echo acquisition is used to collect 160 contiguous 1 mm T1–weighted images in the sagittal plane (TR = 22, TE = 10, flip angle = 30°, 140 1 mm sagittal slices). The rectangular field of view (FOV) for the sagittal images is 256 mm (SI) by 224 mm (AP).

MRI DATA ANALYSIS

VBM was used to investigate morphological differences between the different groups. MRI scans were spatially normalized by linear transformation into a standard stereotaxic Talairach space (Talairach and Tournoux, 1988). They were corrected for intensity non-uniformity (shading artifact) using the N3 software package (Sled et al., 1998). Each voxel was automatically labeled as white matter, gray matter, cerebrospinal fluid, or background using Intensity Normalized Stereotaxic Environment for the Classification of Tissues (INSECT) (Zijdenbos et al., 2002). The skull and dura were then masked from the brain. The gray matter was smoothed using a 8 mm full-width at half-maximum (FWHM) Gaussian kernel. Generalized linear model was used to correlate performance on the CSDLT with gray matter in our regions of interest, namely the hippocampus and caudate nucleus

(Worsley et al., 2002). After this initial analysis, results were used to regress gray matter values from our peak voxel in the hippocampus against the whole brain. This analysis allowed us to examine areas in the brain that co-vary with gray matter in the hippocampus.

Outputs of the statistical analyses were displayed as a statistical map overlaid on an MRI scan. For results within the hippocampus, statistical maps were overlaid on an MRI scan of a spatial learner, categorized by performance on the recombined pairs condition. The statistical maps show regions of gray matter that correlate with our variable of interest. Based on our a priori hypothesis, an uncorrected p-value of 0.001 ($N = 45$, $t = 3.29$) was used for voxels in the predicted regions of interest, namely, the hippocampus and caudate nucleus. For the whole brain, a Bonferroni correction for multiple comparisons was used to calculate the t-statistical threshold ($t = 5.47$ at $p < 0.05$).

RESULTS

BEHAVIORAL

All participants were able to learn the reward contingency of the arms during the encoding phase of the CSLDT. On average participants required 10.02 ± 4.15 trials to reach criteria. Average performance on Stage 2 was 5.55 ± 1.96 out of 8. On the RAVLT, participants were able to recall an average of 10.83 ± 2.76 of the 15 words AI and 10.37 ± 3.38 after the 30-min delay. After the 30-min delay of the RO, participants had an average score of 18.14 ± 6.83 out of 32. Performance on Stage 2 of the CSDLT did not correlate with performance on the RAVLT (AI: $r = 0.012$, $p > 0.05$; Delayed recall: $r = 0.093$, $p > 0.05$) or RO ($r = -0.155$, $p > 0.05$). There was also no correlation between performance on Stage 2 of the CSDLT and age ($r = -0.061$, $p > 0.05$), years of education ($r = 0.019$, $p > 0.05$), or sex ($t = 1.19$, $p > 0.05$).

VBM

Using VBM, performance on the CSDLT was regressed against gray matter in the brain. Performance during the recombined pairs condition (Stage 2) of the CSDLT positively correlated with gray matter in the right hippocampus (MNI space coordinates $x = 26.0$, $y = -37.8$, $z = -3.2$; $t = 3.53$, $p < 0.0005$), suggesting that healthy older adults who have higher scores on the recombined pairs condition and thus use spatial strategies, have more gray matter in the hippocampus (**Figure 2**). The correlation between the peak gray matter value in the hippocampus and performance on the recombined pairs condition of the CSDLT was $r = 0.478$, $p < 0.001$ (**Figure 3**). No areas of the brain, including the caudate nucleus, were found to negatively correlate with the performance on the recombined pairs condition of the CSDLT. In other words, we did not find a correlation between low score on the recombined pairs condition, indicative of a response strategy and gray matter in the caudate nucleus ($p > 0.001$, uncorrected). The number of trials to reach criteria did not correlate with gray matter in the hippocampus or caudate nucleus.

Gray matter values extracted from our peak voxel in the hippocampus (from the first analysis) were used to regress against the entire MRI volume in all participants. Results showed a network of regions known to be anatomically linked to the hippocampus co-varying with the peak voxel in the right hippocampus

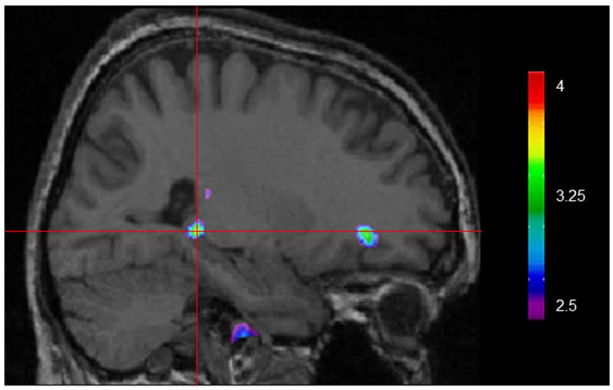

FIGURE 2 | Whole brain regression analysis with scores on recombined pairs condition of CSDLT (Stage 2). Results are superimposed onto an anatomical MRI and displayed in the sagittal plane. Results show that gray matter in the hippocampus significantly co-vary with spatial navigational strategies (MNI space coordinates $x = 26.0$, $y = -37.8$, $z = -3.2$; $t = 3.53$, $p < 0.0005$).

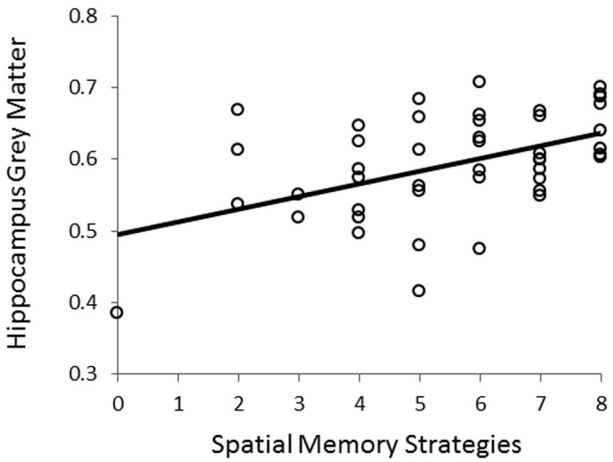

FIGURE 3 | Correlation between scores on the recombined pairs condition (Stage 2) of the CSDLT and gray matter values extracted from the peak voxel (MNI space coordinates $x = 26.0$, $y = -37.8$, $z = -3.2$) in the right posterior hippocampus ($r = 0.478$, $p < 0.001$). This graph shows that a better spatial memory score is associated with increased gray matter in the hippocampus.

(**Figure 4**). Consistent with our earlier findings (Bohbot et al., 2007), with increasing gray matter in the hippocampus, there was increased gray matter in the contralateral hippocampus, the right orbitofrontal cortex, bilateral amygdala, and bilateral parahippocampal cortex.

NEUROANATOMICAL CORRELATES OF NEUROPSYCHOLOGICAL MEASURES

Performance AI and delayed recall on the RAVLT did not correlate with hippocampus gray matter. Similarly, delayed recall on the RO did not correlate with gray matter in the hippocampus

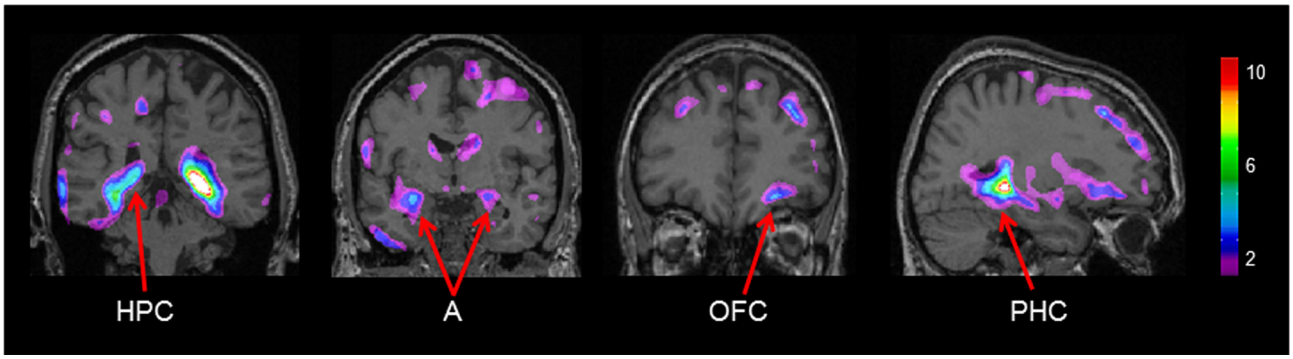

FIGURE 4 | Regions of the brain that co-varied with our peak hippocampal gray matter value ($x = 26.0$, $y = -37.8$, $z = -3.2$). A, Amygdala; HPC, hippocampus; PHC, parahippocampal cortex; OFC, orbitofrontal cortex. The color bar illustrates the range of *t* statistical values.

suggesting that spatial memory is more sensitive to gray matter differences in the hippocampus than other types of memory measured with standard Neuropsychological tests.

DISCUSSION

In the present study, we examined the relationship between performance on a virtual navigation task and gray matter in the hippocampus in healthy older adults. With VBM, we showed that the spontaneous use of spatial memory strategies positively correlates with gray matter in the hippocampus. In contrast, the use of response strategies negatively correlates with gray matter in the hippocampus. When the peak value in the hippocampus, the area in the hippocampus which most highly correlated with spatial memory, was used as a seed voxel to correlate with gray matter in the whole brain, positive correlations were observed in regions that are anatomically and functionally linked to the hippocampus, such as the contralateral hippocampus, the right orbitofrontal cortex, bilateral amygdala, and bilateral parahippocampal cortex.

While some studies in the literature reported a significant relationship between hippocampal volume and spatial memory (Chen et al., 2010; Head and Isom, 2010), others have failed to demonstrate this effect (Driscoll et al., 2003; Moffat et al., 2007). One factor that may help shed light on this issue concerns the fact that none of these studies involved tasks that assessed spontaneous navigational strategies (when both spatial and response strategies can be used in the same task). Indeed, ours is the first structural MRI study to utilize a task in older adults that distinguishes between navigational strategies. This is a notable distinction because both human and non-human animal studies showed that with aging, there is a decreased use of spatial strategies and increased use of response strategies (Barnes et al., 1980; Rapp et al., 1997; Rodgers et al., 2010; Etchamendy et al., 2011). Therefore, older adults tested on the virtual Water Maze (e.g., Moffat et al., 2007) may have performed well on that task despite the fact that they would have used a response strategy dependent on the caudate nucleus when tested on another task allowing for both strategies (Etchamendy and Bohbot, 2007). If this is the case, an association between task performance and hippocampal volume would not necessarily be found. On the other hand, as mentioned above, some spatial memory tasks that did not measure spontaneous navigational strategies were sensitive to gray matter in the hippocampus (Chen et al., 2010; Head and Isom, 2010). Further research would be needed in order to shed light on this issue. For instance, some of these spatial tasks may have been sufficiently complex to detect a learning deficit in participants favoring response strategies, thereby inadvertently dissociating between spatial and response strategies. In support of this hypothesis, we previously reported a correlation between spatial strategies and wayfinding performance in healthy older adults (Etchamendy et al., 2012). This would be consistent with our results that demonstrate that in fact only older adults using spatial strategies, and not those using response strategies, have more gray matter in the hippocampus.

The study by Head and Isom (2010) reported a correlation between caudate nucleus volume and route learning. Route learning is a form of response learning that involves learning a sequence of movements in response to specific stimuli. However, we did not observe a negative correlation between performance and caudate nucleus gray matter with the current task, suggesting that it may not be sensitive enough to detect variability in the gray matter of the caudate nucleus of our population. Interestingly, Kennedy et al. (2009) demonstrated a non-linear decline in hippocampus volume as a function of age, where the rate of hippocampus atrophy accelerates with age, while Raz et al. (2003) showed that in the caudate nucleus, there is a linear decline in volume with aging. Therefore, within an older adult population, there may be more variability in the volume of the hippocampus than in the volume of the caudate nucleus, making it easier to detect morphological differences within the hippocampus. Recruiting participants in a wider age range may help increase sensitivity to morphological differences in the caudate nucleus. Indeed, the age range of the participants in the Head and Isom (2010) study was 56–86 years, while in the current study it was 60–75 years. Therefore, a wider age range of participants may be needed to uncover the relationship between gray matter in the caudate nucleus and response strategies in our task.

We observed an association between the aging hippocampus and response strategies. However, the causal relationship cannot be determined in this study, i.e., the use of response strategies may be the consequence of decreased gray matter in the hippocampus

or it may be the cause of a decrease gray matter in the hippocampus, i.e., "use it or loose it." In other words, biological factors such as genes (Banner et al., 2011) may have a negative impact on the hippocampus leading to an increase use in response strategies. Alternatively, environmental factors such as repetition (which leads to habit) (Iaria et al., 2003), stress (Schwabe et al., 2008), or reward (Del Balso et al., 2010) could promote response strategies at the expense of spatial strategies associated with the hippocampus. It is most likely a combination of both. Importantly, the fact that we found an association between response strategies and the aging hippocampus opens new possibilities for spatial memory-based cognitive interventions toward healthy aging (Bohbot et al., 2011). We have previously shown that strategy use can alter gray matter in the mouse hippocampus (Lerch et al., 2011). In that study, mice trained to use spatial strategies showed increased gray matter in the hippocampus relative to mice trained on the response strategy. Preliminary findings in older adults replicated these findings, demonstrating increased gray matter in the hippocampus after the administration of spatial memory training (Fouquet et al., 2011).

The relationship between navigational strategy and the hippocampus in young adults was previously investigated in Iaria et al. (2003) and Bohbot et al. (2007). Iaria et al. (2003) found that in a task where both strategies can be used, 50% of young adults spontaneously used a spatial strategy while 50% used a response strategy. Furthermore, individuals who used a spatial strategy showed significant fMRI activity in the hippocampus, while those who used a response strategy showed significant fMRI activity in the caudate nucleus, relative to baseline. Bohbot et al. (2007) found that the spontaneous use of spatial strategies was associated with increased gray matter in the hippocampus. The same technique of VBM was used to analyze the results in both Bohbot et al. (2007) and the current study. However, a different navigation task was used to assess navigational strategy. In Bohbot et al. (2007), the 4-on-8 virtual maze task was used while in the current study the CSDLT was used. Consistent results were obtained in the two studies.

Similar to Bohbot et al. (2007), a number of brain areas anatomically linked to the hippocampus correlated with gray matter values extracted from our peak voxel in the hippocampus in older adults, such as the orbitofrontal cortex, the parahippocampal cortex, and the amygdala. It is possible that the co-activity of this network of regions during navigation leads to increased gray matter. It has been suggested that the orbitofrontal cortex in rodents is involved in spatial memory (Vafaei and Rashidy-Pour, 2004) and learning reward expectancy in a spatial context (Young and Shapiro, 2011). Indeed, orbitofrontal cortex neurons respond when a rodent enters an arm that is expected to contain a reward. The parahippocampal cortex is known to be involved in navigation and its functions involve scene processing and spatial learning (Bohbot et al., 1998; Epstein, 2008). In rodents, the amygdala is associated with the hippocampus in place preference learning when it is associated with reward (Gaskin and White, 2006).

We also investigated the relationship between neuropsychological performance and gray matter in the hippocampus. Previous studies have found a correlation between the RAVLT and volume of the left hippocampus (Hackert et al., 2002; Chen et al., 2010), however we did not find this effect in our study. The inconsistency from the literature may arise from a cohort effect. The current sample population is composed of high functioning older adults with no detectable cognitive impairment. The RAVLT and RO may therefore not be sensitive enough to detect differences in gray matter in a more homogeneous population. These results suggest that spatial memory strategies are more sensitive to structural differences in the hippocampus than standard neuropsychological tests. In fact, a prospective study showed that patients with dementia had deficits in spatial cognition that preceded conversion to dementia by 3 years. In the same cohort, verbal memory, and working memory deficits were detected only 1 year before patients were diagnosed with dementia (Johnson et al., 2009), further demonstrating the sensitivity of spatial memory.

In conclusion, our present findings are consistent with the literature reporting that in healthy older adults there is a positive correlation between spatial memory and gray matter in the hippocampus. Furthermore, our results showed that those who have lower hippocampal gray matter are actually using another form of navigational strategy, the response strategy. With whole brain analysis, we observed that individuals with more gray matter in the hippocampus had more gray matter in anatomically and functionally connected cortical areas, namely the contralateral hippocampus, the right orbitofrontal cortex, bilateral amygdala, and bilateral parahippocampal cortex. Future studies will be needed to examine whether an intervention method focusing on spatial memory training can increase gray matter in the hippocampus and anatomically connected areas. Promoting the use of spatial strategies can be a potential avenue for intervention methods against hippocampal atrophy (Fotuhi et al., 2012). As lower hippocampal volume is a risk factor for cognitive decline as well as a number of disorders including Alzheimer's disease (Convit et al., 1997; Rusinek et al., 2003; Tapiola et al., 2008), promoting the use of spatial memory can potentially have protective effects against cognitive deficits in normal aging as well as risks of degenerative disorders of the hippocampus.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 May 2012; accepted: 07 January 2013; published online: 20 February 2013.

*Citation: Konishi K and Bohbot VD (2013) Spatial navigational strategies correlate with gray matter in the hippocampus of healthy older adults tested in a virtual maze. Front. Ag. Neurosci. **5**:1. doi: 10.3389/fnagi.2013.00001*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 15 November 2012
doi: 10.3389/fnagi.2012.00028

Virtual navigation strategies from childhood to senescence: evidence for changes across the life span

Veronique D. Bohbot[1]*, Sam McKenzie[1], Kyoko Konishi[1], Celine Fouquet[1], Vanessa Kurdi[1], Russel Schachar[2], Michel Boivin[3] and Philippe Robaey[4]

[1] Department of Psychiatry, Douglas Institute, McGill University, Verdun, QC, Canada
[2] Hospital for Sick Children, Toronto, ON, Canada
[3] Deptartment of Psychology, Université de Laval, Quebec, QC, Canada
[4] Department of Psychiatry, Ste-Justine Research Center, Montreal, QC, Canada

Edited by:
Thomas Wolbers, German Center for Neurodegenerative Diseases (DZNE), Germany

Reviewed by:
Jacques Micheau, University of Bordeaux 1, France
Jan M. Wiener, Bournemouth University, UK

***Correspondence:**
Veronique D. Bohbot, Faculty of Medicine, Department of Psychiatry, Douglas Mental Health University Institute, McGill University, FBC Building, 6875 boul. LaSalle, Verdun, QC H4H 1R3, Canada.
e-mail: veronique.bohbot@mcgill.ca

This study sought to investigate navigational strategies across the life span, by testing 8-years old children to 80-years old healthy older adults on the 4 on 8 virtual maze (4/8VM). The 4/8VM was previously developed to assess spontaneous navigational strategies, i.e., hippocampal-dependent spatial strategies (navigation by memorizing relationships between landmarks) versus caudate nucleus-dependent response strategies (memorizing a series of left and right turns from a given starting position). With the 4/8VM, we previously demonstrated greater fMRI activity and gray matter in the hippocampus of spatial learners relative to response learners. A sample of 599 healthy participants was tested in the current study. Results showed that 84.4% of children, 46.3% of young adults, and 39.3% of older adults spontaneously used spatial strategies ($p < 0.0001$). Our results suggest that while children predominantly use spatial strategies, the proportion of participants using spatial strategies decreases across the life span, in favor of response strategies. Factors promoting response strategies include repetition, reward and stress. Since response strategies can result from successful repetition of a behavioral pattern, we propose that the increase in response strategies is a biological adaptive mechanism that allows for the automatization of behavior such as walking in order to free up hippocampal-dependent resources. However, the down-side of this shift from spatial to response strategies occurs if people stop building novel relationships, which occurs with repetition and routine, and thereby stop stimulating their hippocampus. Reduced fMRI activity and gray matter in the hippocampus were shown to correlate with cognitive deficits in normal aging. Therefore, these results have important implications regarding factors involved in healthy and successful aging.

Keywords: hippocampus, caudate nucleus, navigational strategy, spatial memory, twins, children, aging

INTRODUCTION

The human brain changes across the entire life span. Throughout childhood there are changes in the function and size of numerous brain structures which correlate with increased performance on tasks that are dependent upon these regions (Casey et al., 2002; Thomas et al., 2004; Menon et al., 2005). In contrast, decreases in memory and executive function have been observed with normal aging. These deficits have been associated with decreases in the volume of the hippocampus (Lupien et al., 1998; Small et al., 2002; Raz et al., 2004; Moffat et al., 2006) and frontal cortex (Raz et al., 1997; Grady and Craik, 2000; Cabeza, 2002). Despite known neural changes that happen during development and aging, very few human studies have examined the corresponding changes in behavior across the entire lifespan.

Navigation is often used as a model for learning because it is possible to dissociate different learning strategies which depend upon distinct memory systems. Many lines of research in rodents and humans have demonstrated that the hippocampus is required when one must learn the spatial relationships between multiple landmarks in the environment, i.e., when forming a cognitive map of the relationships between environmental landmarks (O'Keefe and Nadel, 1978; Packard et al., 1989; Bohbot et al., 2004). On the other hand, when stimulus-response associations must be made, i.e., by learning a series of specific movements from a given start position or stimulus, the striatum, formed of the caudate nucleus, putamen and nucleus accumbens, is necessary. Under certain experimental conditions, recruitment of the hippocampus has actually been shown to interfere with this form of learning (Packard et al., 1989; McDonald and White, 1993; Hartley et al., 2003). In young adult humans, the spontaneous use of a response strategy during virtual navigation has been associated with increased activity and gray matter of the caudate nucleus portion of the striatum, while the use of a spatial strategy has been related to increased activity and gray matter in the hippocampus (Iaria et al., 2003; Bohbot et al., 2007). Interestingly, a negative correlation between the gray matter of the caudate nucleus and hippocampus was observed (Bohbot et al., 2007), a finding that adds to the growing body of literature

describing the fact that only one of the two structures is used at any given time, in a manner that appears competitive (Packard et al., 1989; McDonald and White, 1993; Gold, 2004).

Studies in rodents and humans have suggested that memory deficits in older adults are not uniform and may be specific to the decline of particular structures. In a study by Barnes et al. (1980), it was demonstrated that older rats employed a response strategy to a greater extent than younger rats in a T-maze. Similarly, after young and aged rats learn the location of a submerged platform in the Morris Water Maze, aged rats search more readily for a visible platform in a new location showing bias toward response strategies, as opposed to younger rats who ignore the visible platform and continue searching for the submerged platform in the old target location indicating a bias toward spatial strategies (Rapp et al., 1987). Another study (Nicolle et al., 2003) showed that aged mice were able to use a spatial strategy in the Morris Water Maze when forced to, but predominantly used a response strategy when given the choice. Structural and functional imaging studies have shown hippocampal decline in older adults (Jernigan et al., 2001; Raz et al., 2004; Jernigan and Gamst, 2005; Walhovd et al., 2005; Moffat et al., 2007; Head and Isom, 2010) as well as inferior performance when using processes which depend upon the hippocampus, such as spatial memory (Newman and Kaszniak, 2000; Moffat et al., 2006) and episodic memory (Maguire and Frith, 2003; Persson et al., 2006). Etchamendy et al. (2012) showed that human older adults tested on a virtual analog of a rodent radial task were impaired at using spatial relationships to solve the task, while response learning was intact.

A study (Leplow et al., 2003) has addressed the question of which memory system is spontaneously used in children. In this study, all the children over the age of 10 years old used a spatial strategy. However, it is unclear whether the paradigm used was equally sensitive to the two strategies. Other studies which have not tested for response strategies have found that the development of spatial competence emerges between seven and 8 years of age; about the same time that children can abstract spatial relationships to scaled models (Overman et al., 1996). It is unknown whether school-aged children would depend more on the information processing of the hippocampus or that of the caudate nucleus on a task which can be solved equally well using either learning strategy.

In order to assess the relative contribution of different memory systems across the lifespan, we administered a virtual navigation task that can be learned using either a spatial or response strategy to 299 children, 175 young adults, and 125 older adults. Based on previous studies in rodents and preliminary data with humans from our laboratory, we predicted that children would predominantly use spatial strategies and that response learning strategies would be increasingly used with age.

METHODS

PARTICIPANTS

Children participants were taken from a sample of 299 eight-years-old twins (monozygotic and dizygotic). Ninety-five young adults who took part in four ongoing studies were added to the sample of 80 young participants tested in two previously published studies (Iaria et al., 2003; Etchamendy et al., 2007) in which the same paradigm was used. Only data from the behavioral studies were used for the current study. In total, 175 young adults (84 men, 91 women, mean age: 25.6 ± 4.6 years, age range: 19–40) were tested. Participants were recruited through word of mouth. A sample of 125 older adults (50 men, 75 women, mean age: 66.5 ± 6.6 years, age range: 53–85) were recruited from newspaper and radio ads.

All participants were screened for neurological and psychiatric disorders, including depression. All older adult participants scored above the normative cutoff score for the Mini Mental State Examination (Iverson, 1998). All participants gave written consent to take part in the study. In the case of child participants, written consent was obtained from the parents. The study was approved by the Research Ethics Board at the Douglas Mental Health University Institute and the Sainte-Justine University Hospital Research Center. Participant recruitment and testing was in conformity with the local ethics committee requirements.

4 ON 8 VIRTUAL MAZE (4/8VM)

Adult version

A commercially available computer game (Unreal; Epic Games, Raleigh, NC) was used to create the virtual environments. The virtual tasks were presented on a 17′ computer screen. Before testing, the participants spent a few minutes moving in a virtual room that was different from the experimental environment to practice the motor aspects of the task. When the participants were comfortable using the keypad, the experimenter gave the instructions, and the experiment started.

The 4/8VM is composed of an eight-arm radial maze with a central starting location (**Figure 1**). The maze is surrounded by a landscape (mountains and sunset), two trees, and a short wall located between the landscape and the trees. At the end of each arm are stairs that lead to a pit where, in some of the arms, an object can be picked up. The location of the target objects cannot be seen from the center of the maze. Landmarks in the environment were not located directly in front of the target

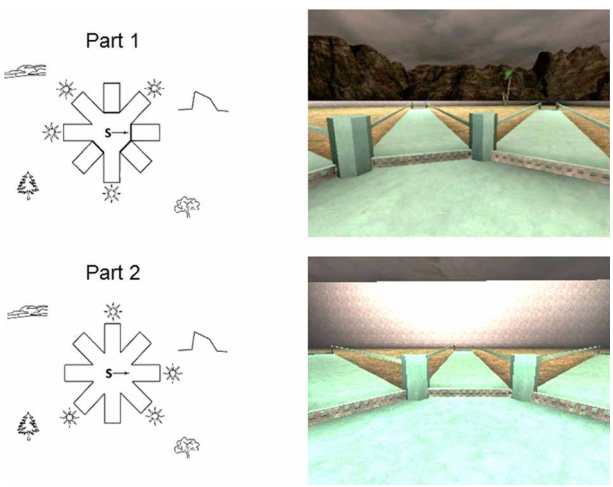

FIGURE 1 | Schematic drawings (left) and first person views (right) of the adult 4/8VM environment.

pathways, thereby avoiding the use of a beacon strategy. The participants used a keypad to move forward, left, and right within the environment and were instructed to not use the backwards key. Participants always started a trial at the center of the radial maze facing the same direction. The 4/8VM consisted of five trials, all of which are composed of two parts. In Part 1 of each trial, four arms were blocked with barriers and the remaining four arms were accessible and contain objects. In Part 2, all arms were accessible and the objects were located in the four arms that were previously blocked in Part 1. The participants were asked to retrieve all objects found in the accessible arms in Part 1 and to remember which arms they visited. In Part 2, they were asked to avoid the arms they previously visited in order to find the objects. Errors consisted of entering into an arm that did not contain an object or revisiting an arm. A trial was completed after all four objects were picked up. Among the five trials, there were three types of trials: type A, B, and C. In Part 1 of trial type A, arms 1, 3, 4, and 6 were accessible and contained objects; in Part 2, the four objects were located at the end of the four previously blocked arms (i.e., arms 2, 5, 7, and 8). In trial type B, a different sequence of accessible arms were used. In Part 1, arms 2, 3, 7, and 8 were accessible, and in Part 2 the objects were located at the end of arms 1, 4, 5, and 6. Trial type C was a probe trial. Part 1 of the probe was identical to part 1 of trial type A. In Part 2, however, the walls around the radial maze were raised to conceal the landscape, and the trees were removed so that no landmarks were visible. During part 2 of the probe trial, all of the arms contained an object. The probe trial was used to distinguish whether participants used a spatial or response strategy to learn the task. If participants were using a spatial strategy in which the landmarks present in the environment were relevant to perform the task, removing the landscape and landmarks should result in an increase in errors. In contrast, if participants were using a response strategy, no increase in errors should occur during the probe trial, since participants would remember a pattern or series of turns in relation to a starting position without relying on the landmarks. To reach criterion and to be allowed to take part in the probe trial, participants were required to make no errors on Part 2 in one of the trials before the probe. The learning criterion was set to ensure that participants were able to learn the task before performing the probe trial which evaluates how they learned the task. Participants were presented with sequences in the order of trial type ABACA. For the young and older adults, data from several studies were combined in order to obtain a larger sample size. Although there were design differences for each of the studies, the portion of the 4/8VM used in the current paper was identical in all studies. In one study, 74 participants received the ABACA sequence whereas in another 50, 13 trials were administered after the ABACA sequence for a total of 18 trials. In the current paper only the ABACA sequence was considered. Participants who were not able to complete a trial without error within the first three trials were given up to two extra trials in order to reach criterion. The extra trials were trial type A.

As previously described (Iaria et al., 2003; Bohbot et al., 2007, 2011; Banner et al., 2011; Andersen et al., 2012), the participants were debriefed at the end of the experiment. They were asked to report how they solved the task from the beginning to the end of the experiment. Participants were classified based on their spontaneous navigational strategy. Participants were categorized as using a response strategy if they initially learned the task by associating the arms with numbers or letters, or by counting the arms (clockwise or counterclockwise) from a single starting point. If they initially used two or more landmarks and did not mention a response strategy, they were categorized as using a spatial strategy. Errors on the probe trial were used to confirm navigational strategies in an objective fashion, where spatial learners were expected to make more errors than response learners. A recent eye tracking paper further validated verbal reports as a method of categorization (Andersen et al., 2012). The study showed that spatial learners spend significantly more time looking at landmarks than response learners.

Children's version

The 4/8VM described above was also used to test children, however the following modifications were necessary in order to obtain a valid test measuring navigational strategies. The environment contained the same eight-arm radial arm maze surrounded by a landscape (mountains and sunset) and two trees, however, additional landmarks were added: a planet, a pyramid, and a pile of boxes. In addition, instead of presenting Part 1 and Part 2 as we did in one trial of the adult version, one trial in the children's version only consisted of Part 2 where all eight arms are accessible and four objects had to be found. Furthermore, only two types of trials were used for the children: trial types A and C (**Figure 2**). This modification was made gradually throughout 1.5 years of pilot studies in order to make the test more easily comprehensible and feasible to 8-years old children. In the children 4/8VM, participants were asked to retrieve all objects from the target arms out of the eight open arms. A trial was completed after all four objects were picked up. The target arms were the same arms as those used in the adult version (2, 5, 7, and 8). Due to time constraints, participants were given at most either 10 (version 1, $N = 51$) or 13 trials (version 2, $N = 209$) to learn the target arms (2, 5, 7, and 8) to criteria. As in the adult version, at the beginning

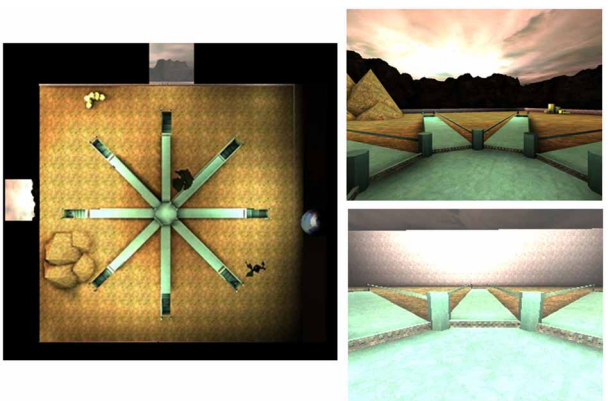

FIGURE 2 | Top down (left) and first person (right) views of the children 4/8VM environment.

of each trial, participants started in the center of the maze facing the same direction. To reach criteria, participants were required to have completed three out of four trials without error. Participants were therefore required to complete a minimum of three trials. For the participants who reached criteria, a second stage of the task, the probe trial (type C), was presented. In the probe trial, similar to the adult version, walls were raised to conceal the landscape and all landmarks were removed. An object was present in every arm. As in the adult version of this task, the purpose of the probe trial was to distinguish the participants who relied on landmarks (i.e., used a spatial strategy) from participants who learned the pattern of target arms irrespective of landmarks (i.e., used a response strategy).

After participants completed the virtual radial arm maze, they were asked how they found each of the objects, following a similar procedure as in adults. Participants were categorized as using a response strategy when they mentioned numbering or counting arms from a given start position, in order to find all the objects (i.e., "I went down the arm directly ahead, the one next to it, then skipped two arms to the right, then skipped one arm"). On the other hand, if participants mentioned at least two landmarks and did not mention using a pattern (i.e., "One was beside the pyramid, one on each side of the tree and one next to the Earth"), they were categorized as using a spatial strategy. The self-reports from the children were less detailed than those of the young and older adults. In order to prevent misclassifications, verbal reports that were ambiguous (e.g., when participants could only report a strategy to find one or two of the goal arms) or did not describe a strategy (e.g., "I just remembered where the arms were") were excluded. This method of categorization proved to be effective, as we were able to classify 86.48% of our participants.

Errors on the probe trial were used to confirm navigational strategies in an objective fashion. Again, participants using a spatial strategy were expected to make more errors that those using a response strategy, since they relied more on landmarks to find the objects.

In summary, as in the adult study, children were required to remember the position of four objects located in four of the eight arms during acquisition of the task and were required to reach criterion before the administration of the probe trial. The probe trial was used to assess navigational strategy and involved having to retrieve four objects in four of the eight arms in an environment devoid of landmarks and with a hidden landscape.

ANALYSIS

All analyses were done using SPSS version 15.0 and Microsoft Office Excel 2003. For all participants, task performance was measured by analyzing the total number of errors made when participants had to remember which of the eight open arms contained objects (i.e., Part 2 of each trial). Part 1 errors were not taken into account because errors in a four-arm environment do not provide a sensitive measure of learning and memory for adults and because Part 1 was not administered to children.

During the probe trial, most of the participants in all age groups had the impulse to look around before making their selection and lost their initial heading. Consequently, the pattern of visited arms was used to score errors on the probe trial instead of using the actual arms in absolute space. This was assessed by rotating the pattern of visited arms until we obtained the best match. This method allowed us to distinguish individuals who had learned the pattern of arms (i.e., the response learners) from those who had used the spatial strategy. Specifically, we calculated a probe error term by considering what the number of errors would be if the goal arms were rotated to new positions around the radial arm maze. For example, the goal arms in absolute space were 2, 5, 7, and 8. If a participant initially turned 12.5° clockwise (one arm) and followed the learned relationships between the goal arms thereby making zero errors, they would enter arms 3, 6, 8, and 1, which, if errors were considered in absolute space, would result in three errors. The goal arms were rotated seven times for each possible initial shift in point of view. The best probe error term was then used for further data analysis for all participants. Based on all the possible combinations a participant can make, there is an 8.6% chance of getting two errors randomly, 11.4% chance of getting zero errors randomly, and 80% chance of making one error. Therefore, the mean rotational errors someone can make if they choose randomly is one. Verbal reports were scored by two independent raters showing a 99% agreement in the assessment of strategies for older adults, 93% for young adults and 93% for children.

RESULTS

PERFORMANCE

Children

Of these 299 children tested on the virtual radial arm maze, 281 had verbal report and we were able to assess spontaneous strategy in 243 children in total. Of the 299 original participants, 14 children were given the possibility to make 16 choices per trial instead of eight choices. Their verbal reports were analyzed but, to avoid any bias, their performance on the acquisition of the task was not included in the analysis. Among the remaining 285 children tested on the same version of the task (eight choices maximum per trial), 25 participants were excluded due to nausea ($N = 7$), failure to cooperate ($N = 10$), experimental error in administering the task ($N = 1$), and failure to complete the task within the allotted time ($N = 7$). The final sample used for analysis ($N = 260$) consisted of 134 boys and 126 girls and the average age for boys and girls combined was 8.43 ± 0.11 years old.

In total, of the 260 children who completed the study, 205 (78.8%) reached criteria, and 199 completed the probe; six participants who reached criteria did not complete the probe due to time constraints. Children made an average of 6.36 errors ($SD = 3.53$) on the first trial, 3.83 errors ($SD = 1.79$) on the second trial, and 3.05 errors ($SD = 2.08$) on the third trial. Of the 299 children tested, we were able to classify the spontaneous strategies of 243 participants. Of the 243 children, 205 used a spatial strategy (84.4%) and only 38 (15.6%) reported using a response strategy. Children's learning strategy had a profound effect on performance during the probe trial, confirming that our assessment of navigational strategy is consistent with errors on the probe trial. Those that reported using a response strategy made significantly fewer probe errors than those who reported using a spatial strategy, (response mean = 0.69, $SD = 0.59$; spatial mean = 0.90, $SD = 0.65$; one-tail

independent samples t-test, $p < 0.05$), indicating that response learners relied less on environmental landmarks than spatial learners.

Note that among the 260 children included in the analysis, 51 children were given at most 10 trials (version 1) to reach criteria while 209 were given 13 trials (version 2) to reach criteria. The version of the task did not influence the proportion of children who reached criteria (80.4% in version 1 and 78.5% in version 2) or the average number of errors made during the first 3 trials (4.6 ± 1.7 in version 1 and 4.4 ± 1.7 in version 2). The strategy spontaneously used by the children was also not affected by the version of the task. Spatial strategy was used by 93.2% of the children who were tested on version 1 and 82.01% of the children who were tested on version 2 (chi-square, $p > 0.05$). Taken together, these results indicate that the number of trials given to reach criteria did not influence neither the acquisition of the task nor the strategy used to solve it. Children data from both versions were therefore pooled together for the analyses.

Young adults

Of the 175 young adults, seven young adults did not meet criteria by the third trial. At the time of testing these participants were not given extra trials to learn the task before the probe, and therefore their probe performance were not considered in the analysis. Of the 175 young adults, error scores on the learning trials were not available for five participants, however, these participants reached criteria and therefore their strategy and probe scores were included in the analysis. In addition, eight participants did not perform the probe trial although criterion was met.

Young adults made an average of 1.54 errors ($SD = 2.27$) on the first trial (Trial type A), 0.45 errors ($SD = 1.15$) on the second trial (Trial type B), and 0.37 errors ($SD = 0.9$) on the third trial (Trial type A). Of the 175 young adults, 81 (46.3%) reported the use of a spatial strategy and 94 (53.7%) reported using a response strategy. These percentages are consistent with previous reports (Iaria et al., 2003; Etchamendy et al., 2007). Strategy predicted the number of errors made on the probe trial (one-tail independent samples t-test $t = -3.308$, $p < 0.001$), whereby response learners made fewer probe errors than spatial learners (response mean = 0.18, $SD = 0.45$, spatial mean = 0.47, $SD = 0.6$), confirming once again that our assessment of navigational strategy is consistent with errors on the probe trial.

Older adults

From the sample of 125 participants, 13 participants in total were excluded due to nausea ($N = 4$), failure to complete the task within the allotted time ($N = 5$) and failure to comprehend the task ($N = 4$). We were able to assess spontaneous strategy in 112 older adults (46 men, 66 women; mean age: 66.5 ± 6.7 years).

Of the 112 older adults, 32 subjects did not reach criteria within the first three trials and needed extra trials, of those 16 older adults never met criteria and did not do the probe trial. Older adults made an average of 2.92 errors ($SD = 2.88$) on the first trial (Trial type A), 2.37 errors ($SD = 2.58$) on the second trial (Trial type B), 1.82 errors ($SD = 2.6$) on the third trial (Trial type A). Of the 125 older adults tested, we were able to classify the spontaneous strategies of 112 participants. Of these 112 older adults, only 44 (39.3%) reported the use of a spatial strategy and 68 (60.7%) reported the use of a response strategy. Reported strategy predicted the number of probe errors (response mean = 0.37 errors, $SD = 0.55$; spatial mean = 0.72 errors; $SD = 0.70$; one-tail independent samples t-test $t = 2.76$, $p < 0.01$), confirming once again that our assessment of navigational strategy is consistent with errors on the probe trial. In the event that giving additional trials could influence navigational strategy, a separate analysis was performed with only the older adult participants who reached criteria in three trials. Results showed that the proportion of spatial and response learners did not differ from the whole group analysis: 62.4% used a response strategy and 37.6% used a spatial strategy. Therefore, giving older adult participants extra trials did not affect their navigational strategy. In support of these findings, giving extra trials to children did not increase their rate of using a response strategy. We further argue that a shift toward response strategies only occurs with over-training, after participants perform the task to criteria.

Children, young adults and older adults

When looking at all of the participants, 199 children, 160 young adults, and 96 older adults reached criteria and performed the probe trial. There was a significant difference in performance between children, young adults, and older adults on the first three learning trials [$F_{(2,\ 540)} = 298.76$; $p < 0.0001$]. During the learning trials, participants had to avoid the arms that they had previously visited in order to retrieve the objects. Young adults made significantly fewer errors than the older adults and both groups performed significantly better than the children (*post-hoc* tests: $p < 0.001$). All participants who met criteria obtained a perfect score in at least one learning trial before the probe. On the last trial, children that reached criteria and did the probe made no errors. Older adults made an average of 0.65 errors ($SD = 1.89$) and young adults made an average of 0.37 errors ($SD = 0.9$) on the last trial before the probe.

STRATEGY

Children

Among the 199 children who reached criteria and did the probe, we were able to assess spontaneous strategy in 191 participants. Within these 191 children, we found that 83.3% were spatial learners and 16.7% were response learners. These proportions are similar to those found when looking at the 281 participants who had verbal report and no probe score. Strategy did not predict performance on the acquisition of the 4/8VM (before the probe trial). Strategy did not influence the number of errors made during the first three trials (independent samples t-test, $p > 0.05$). Similarly, strategy did not affect the number of trials needed to reach criteria (independent samples t-test, $p > 0.05$ in both versions of the task). There was no relationship between sex and strategy in the children population (chi-squared, $p > 0.05$).

Young adults

As in the children sample, strategy did not predict the number of errors made during the first three trials [$F_{(2,\ 167)} =$

0.065, $p > 0.05$]. There was no relationship between sex and strategy in the young adult population (chi-square, $p > 0.05$).

Older adults

Strategy had no effect on performance as measured by the number of errors made in the first three trials [$F_{(2, 107)} = 0.28$; $p > 0.05$]. Strategy also did not predict the decrease in errors between the first and second A trials ($t = 0.208$; $p > 0.05$). Strategy did not interact with older adults' ability to reach criteria by the third trial (chi-square; $p > 0.05$). There was no relationship between sex and strategy in the older adult population (chi-square, $p > 0.05$).

Comparison of the strategies of children, young adults, and older adults

A 3×2 chi-square (children, young adults, older adults × spatial, response) was used to compare the proportion of spatial and response learners across all age groups. The chi-squared analysis revealed a significant interaction [$\chi^2 = 94.69$, $p < 0.0001$] between age and strategy, with a decrease in the use of a spatial strategy throughout the lifespan: 84.4% of children, 46.3% of young adults, and only 39.3% of older adults reported the use of a spatial strategy (**Figure 3**). *Post-hoc* analysis revealed a significant difference in the proportion of spatial and response learners between children and young adults [$\chi^2 = 68.26$, $p < 0.0001$] and children and older adults [$\chi^2 = 74.38$, $p < 0.0001$]. There was no significant difference in the proportion of spatial and response learners between young and older adults [$\chi^2 = 1.361$, $p > 0.05$].

The probe trial was successful at discriminating between spatial and response strategies. A 3 × 2 ANOVA (age × strategy) revealed a significant main effect of strategy on probe performance [$F_{(2, 447)} = 9.96$, $p < 0.001$]. As anticipated, there was no interaction between age and strategy because response learners performed better than spatial learners on the probe trial across all ages [$F_{(1, 447)} = 0.221$, $p = 0.638$]. In order for the groups to be comparable, a normalized error term was calculated for each individual such that the average probe error equals one in each group. **Figure 4** shows the normalized probe errors according to strategy and age group.

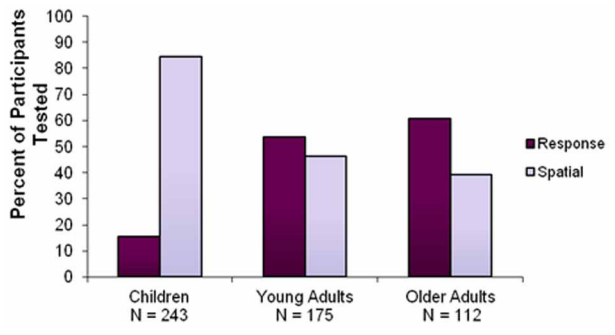

FIGURE 3 | Percentage of participants using a spatial or response strategy according to age group. This graph shows that the use of response strategies increases across the life span, at the expense of spatial strategies.

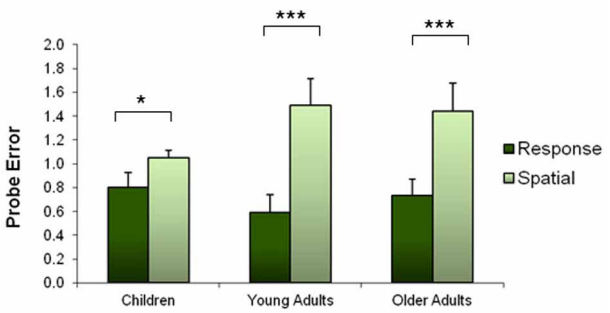

FIGURE 4 | Normalized mean number of probe errors according to strategy and age group. This graph shows that probe errors were effective at dissociating spatial and response strategies: spatial learners made more errors on the probe trial than response learners. Error bars represent standard error of the mean. *$p < 0.05$; ***$p < 0.001$.

DISCUSSION

Our findings demonstrate a shift in navigational strategy across the lifespan (**Figure 3**). We found that 84% of children reported using a spatial strategy, indicating a clear bias compared to the 47% of young adults who reported using the same strategy. We also observed that 39% of older adults used a spatial strategy. Moreover, we found that response learners performed better on the probe than spatial learners in every age group, a finding which extends the results of previous studies carried out in young adults (Iaria et al., 2003; Bohbot et al., 2007) to children and older adults (**Figure 4**). These results suggest that, across all age groups, the probe trial was effective in discriminating spatial learners who relied on environmental landmarks from response learners who were not as affected by the removal of landmarks.

Young adults performed better than older adults on trials 1, 2, and 3, which is consistent with general navigational deficits that have been observed in normal aging (Marighetto et al., 1999; Driscoll et al., 2005). While some caudate nucleus-dependent deficits have been observed with aging (Barrash, 1994; Wilkniss et al., 1997; Meulenbroek et al., 2004; Raz and Rodrigue, 2006; Head and Isom, 2010), human and animal studies show that these deficits are milder or relatively spared in old age (Vasquez et al., 1983; Grady and Craik, 2000; Churchill et al., 2003). Bach et al. (1999) tested young and old mice on a Barnes circular maze and found that old mice had deficits in spatial memory compared to young mice. The same study also showed that on a cued version of the same task, a version that requires the formation of stimulus-response associations, aged mice performed similar to young mice, demonstrating the sparing of response learning with age. Interestingly, during learning, after the initial random exploration, aged mice adapted a serial search strategy that does not rely on the hippocampus while young mice adapted a spatial search strategy dependent on the hippocampus. Rapp et al. (1997) found similar results in monkeys where older monkeys used a serial search strategy compared to young monkeys. Authors also found that older monkeys were not affected by the removal of external maze cues, demonstrating their lack of reliance on spatial landmarks. Our study translates these results to humans and reveals a more complex picture for cognitive aging. The

deficit seen in normal older adults in the current study is paralleled with a shift toward using response strategies, an effect first demonstrated in rats by Barnes et al. (1980). Response strategies are efficient when navigating in an environment where the start and target locations are constant, as in route learning paradigms (Hartley et al., 2003; Iaria et al., 2003; Head and Isom, 2010). In contrast, when the relationship between the start and target position changes and a novel path must be derived, response strategies are inefficient (Hartley et al., 2003; Driscoll et al., 2005). Deriving a novel path from different start and target locations requires knowledge of a cognitive map, making the use of spatial strategies more efficient. The drive toward efficiency may be an important underlying factor behind the shift in strategies with normal aging. With the repetition of a successful behavior, a response strategy emerges, leading to the automatization of behavior or habit formation (Iaria et al., 2003). However, this shift toward response strategies comes at a cost when a novel path must be derived using a cognitive map in order to navigate successfully.

Other lifestyle factors can produce a shift from using spatial strategies to response strategies with aging. For example, stress, as well as addiction related rewards such as nicotine, opiates, psychostimulants, and alcohol have been shown to affect the integrity of the hippocampus. Stress was reported to impair the hippocampus through the actions of glucocorticoids (Sapolsky et al., 1990; Sapolsky, 1994; McEwen and Sapolsky, 1995; Conrad et al., 1996; McKittrick et al., 2000; Kleen et al., 2006) and was shown to have an effect on navigational strategies. Schwabe et al. (2007, 2008, 2010, 2012) found that chronic stress, acute stress, and prenatal stress can increase the use of response strategies in people tested on a navigation task. Taking into consideration the inverse relationship between hippocampus and caudate nucleus gray matter (Bohbot et al., 2007) and the fact that rewards stimulate the caudate nucleus, we can expect the probability of using caudate nucleus-dependent response strategies to be higher in people exhibiting reward-seeking behaviors. Supportive evidence is found in a study showing that rewards lead to increased goal-oriented navigation and decreased free exploration, the latter of which is characteristic of spatial memory, in healthy adults performing a virtual water maze task (Adcock, 2010). These studies demonstrate that stress and reward can promote the use of response strategies.

Children, including both spatial and response learners had a higher number of probe errors than adult spatial and response learners. These data support the finding that children preferentially use their hippocampus to navigate, since high probe errors have been shown to be associated with greater hippocampal involvement (Iaria et al., 2003). Even the children that used caudate nucleus-dependent response strategies over hippocampus-dependent spatial strategies showed higher probe deficits as compared to young adults, suggesting that response learning may also be immature at 8 years of age. As an alternative to the view that the striatum is mature by childhood (Reber, 1992; Maybery and O'Brien-Malone, 1998), we propose that response learning, especially in difficult tasks, may also continue to develop through childhood and adolescence (Casey et al., 2002; Sowell et al., 2002; Thomas et al., 2004). Although children are capable of using patterns to learn, the pattern formation required in the current task that leads to the use of a response strategy, is much more sophisticated compared to a simple "egocentric" strategy, involving a single vector addition from a given position, reported in numerous children studies (Overman et al., 1996; Bremner and Bryant, 1977). As opposed to navigating toward a beacon, successful probe performance in our task requires participants to keep in memory a sequence of movements through virtual space. In other tasks that require more complex sequence learning, children have been shown to be impaired relative to adults and there is increased activation in the caudate nucleus when age is correlated with performance (Thomas et al., 2004). Though children may be capable of using an egocentric strategy from a very young age, even before the emergence of spatial strategies (Lehnung et al., 1998), the complex pattern of stimulus-response associations required in the current task seems to evolve later on.

Unlike previous reports that used tasks for which all adults used a spatial strategy (Bullens et al., 2010), we have shown that in learning situations where young adults are equally likely to adopt a spatial strategy or a response strategy, children are biased toward using spatial strategies. It is of interest that we found spatial strategies dominating in childhood, since these results show a bias toward hippocampal-based learning in the early stages of life, despite the immaturity of the hippocampus (Saitoh et al., 2001; Pine et al., 2002; Mulani et al., 2005; Lavenex et al., 2007). We recently replicated these findings in children using identical testing environments. We showed that 7–9 years old children use spatial strategies in greater proportions than older participants who in this case were older children 10–18 years of age (Lin et al., 2012). The caudate nucleus is a slow learning system that develops habits through repetition across a session (Iaria et al., 2003; Orban et al., 2006), days (Packard and McGaugh, 1996; Barnes et al., 2005), and potentially much longer periods of time depending on the complexity of the task. In childhood, most experiences are new and thus children have a smaller repertoire of habits because they have less experience in the world than adults. We hypothesize that this paucity of repetitive behavior is the reason we found a smaller proportion of children using caudate nucleus-dependant response learning and a greater percentage using hippocampal-based spatial learning. Interestingly, in young preweanling rats, the existence of place, head-direction, and grid cells have been shown even before rat pups begin exploring an environment. This finding demonstrates that the mechanisms necessary for building cognitive maps exist early on in development (Wills et al., 2010).

The traditional view that older adults tend to use response strategies because of an aging process, which negatively affects the hippocampus, suggests a compensatory mechanism for this shift in strategies (Etchamendy et al., 2012). We offer an alternate hypothesis whereby a shift in navigational strategy with time is a consequence of the increased use of the caudate nucleus-based response learning in older adults (Balram et al., 2010). We suggest that it is biologically adaptive for the caudate nucleus to automatize frequently repeated behavioral and cognitive processes such as learning how to walk, in order to free up cognitive resources (Albouy et al., 2008, 2012). This process, however, will result in a bias toward the memory encoding strategies dependent on the caudate nucleus and decrease the need to make novel relationships between multiple stimuli, a process which requires

the hippocampus (Eichenbaum et al., 1992). With aging, people often gain expertise in a specific field through professional and personal life experiences. Gaining expertise, however, often involves carrying out processes faster and more efficiently. We argue that repetitive day-to-day behavior decreases the likelihood of experiencing difficult and long processes normally required for learning new things.

Normal aging is accompanied by a decrease in hippocampal volume and functional activity, which is associated with navigational deficits (Driscoll et al., 2005) in spatial memory tasks (Moffat et al., 2006; Antonova et al., 2009; Chen et al., 2010; Head and Isom, 2010). We suggest that decreases in hippocampal volume and activity could be a consequence of increased use of response strategies. In fact, recent studies by Rodgers et al. (2012) and Etchamendy et al. (2012) showed that a larger proportion of older adults use response strategies compared to young adults. When middle age healthy participants (mean age $= 43.0 \pm 5.9$ years) were tested as a control group for patients with damage to the hippocampus in Bohbot et al. (2004), 85% used a response strategy on the 4/8VM. Although in the current study we did not find a direct difference in the proportion of spatial and response learners between young and older adults this may in part be due to stringent screening for various disorders, more common in older adults than in young adults. In Bohbot et al. (2004) healthy participants were recruited by word of mouth and were often spouses of the brain-damaged patients because they were balanced for age, education and socio-economic status. On the other hand, participants recruited for studies comparing young and older adults have to be screened for numerous factors. This screening process results in a greater exclusion rate in older adults than in young adults making the older adult population a very healthy sample, free of neurological, psychiatric, metabolic (e.g., heart attack, cholesterol, diabetes), and chronic diseases (e.g., cancer). As previously mentioned, the automatization of behavior may be a biologically adaptive mechanism that permits us to free up resources, such as hippocampal function. However, less hippocampal engagement may lead to decreased hippocampal gray matter and volume, which is associated with cognitive deficits in normal aging and is a risk factor for developing dementia (Lupien et al., 1998; Tisserand et al., 2004). This suggestion fits with the finding that years of education lowers the risk of developing dementia (Ravaglia et al., 2002; Karp et al., 2004; Caamano-Isorna et al., 2006), presumably because the hippocampus was involved in making novel relationships for a longer period of time while people were learning new information. Thus, having more years of education may play a role in delaying the shift toward response strategies. Similarly, James et al. (2011) found that people with a larger life space, measured by more movement through the Chicago area during their daily activities, have a decreased risk of developing dementia. Longitudinal studies of successful aging have also highlighted the importance of participating in everyday activities which require the learning of novel information (Hultsch et al., 1999), a finding which gives credence to the "use it or lose it" hypothesis presented here. In support of these studies, our mouse imaging study showed an inverse relationship between gray matter in the hippocampus and striatum when mice trained on a spatial memory version of the water maze were contrasted to mice trained on the response memory version in absence of the possibility of using spatial strategies because landmarks were hidden with a curtain (Lerch et al., 2011). In sum, the use of spatial strategies may have protective effects on the hippocampus.

In conclusion, with age, people who use response strategies to a great extent in their everyday life may be more at risk of developing cognitive deficits in normal aging and dementia (Dossa et al., 2010), through increased caudate-dependent learning and decreased hippocampal-dependent processing. An emphasis on cognitive mapping may increase the functioning and gray matter of the hippocampus, both of which increase the probability of healthy and successful aging. Thus, reversing the shift toward response strategies that comes with age with spatial memory training may be an effective method of prevention against cognitive decline and dementia.

ACKNOWLEDGMENTS

This project was funded CIHR Grant, #64381, #82638, #86727, and CIHR New Emerging Team KIDNET. We wish to thank Louisa Dahmani for her help with the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 May 2012; accepted: 09 October 2012; published online: 15 November 2012.

*Citation: Bohbot VD, McKenzie S, Konishi K, Fouquet C, Kurdi V, Schachar R, Boivin M and Robaey P (2012) Virtual navigation strategies from childhood to senescence: evidence for changes across the life span. Front. Ag. Neurosci. **4**:28. doi: 10.3389/fnagi.2012.00028*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 01 November 2012
doi: 10.3389/fnagi.2012.00029

Aging specifically impairs switching to an allocentric navigational strategy

***Mathew A. Harris*[1,2]*, *Jan M. Wiener*[3] *and Thomas Wolbers*[1,2,4]**

[1] *Centre for Cognitive and Neural Systems, University of Edinburgh, Edinburgh, UK*
[2] *Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK*
[3] *Psychology Research Centre, Bournemouth University, Poole, UK*
[4] *German Center for Neurodegenerative Diseases, Otto-von-Guericke University, Magdeburg, Germany*

Edited by:
Emma R. Wood, University of Edinburgh, UK

Reviewed by:
Weimin Mou, University of Alberta, Canada
Hugo Spiers, University College London, UK

****Correspondence:***
Mathew A. Harris, Centre for Cognitive and Neural Systems, University of Edinburgh, 1 George Square, Edinburgh, EH8 9JZ, UK.
e-mail: m.a.harris-2@sms.ed.ac.uk

Navigation abilities decline with age, partly due to deficits in numerous component processes. Impaired switching between these various processes (i.e., switching navigational strategies) is also likely to contribute to age-related navigational impairments. We tested young and old participants on a virtual plus maze task (VPM), expecting older participants to exhibit a specific strategy switching deficit, despite unimpaired learning of allocentric (place) and egocentric (response) strategies following reversals within each strategy. Our initial results suggested that older participants performed worse during place trial blocks but not response trial blocks, as well as in trial blocks following a strategy switch but not those following a reversal. However, we then separated trial blocks by both strategy and change type, revealing that these initial results were due to a more specific deficit in switching to the place strategy. Place reversals and switches to response, as well as response reversals, were unaffected. We argue that this specific "switch-to-place" deficit could account for apparent impairments in both navigational strategy switching and allocentric processing and contributes more generally to age-related decline in navigation.

Keywords: aging, spatial navigation, strategy switching, allocentric processing, virtual reality, plus maze

INTRODUCTION

Cognitive faculties deteriorate in both normal aging and dementia, and navigation abilities may be among those most severely affected. Brain areas associated with navigation, including the hippocampus and entorhinal cortex, show more extensive degradation in aging and dementia than other brain regions (Driscoll et al., 2003; Du et al., 2003, 2006), and show reduced functional activation during navigation with age (Moffat et al., 2006). Furthermore, some research has confirmed that aging does impair navigational processes specifically dependent on these areas, such as cognitive mapping (Moffat and Resnick, 2002; Iaria et al., 2009) and path integration (Allen et al., 2004; Mahmood et al., 2009; Harris and Wolbers, 2012). These navigational processes are in turn dependent on a range of more fundamental processes (memory, perception, attention, movement control, etc.) also affected by aging. Some aspects of navigation, such as retracing a learned route, seem less susceptible to aging (Jansen et al., 2010), and as many complex navigational processes decline with structural changes such as hippocampal atrophy (Nedelska et al., 2012), older people may be forced to rely on these intact simpler mechanisms (Wiener et al., submitted). However, there are still further aspects of navigation that may be affected by aging but have not yet been well explored. For example, in everyday navigation we do not usually rely solely on any single navigational process; instead we must constantly switch between various different navigational strategies, such as following a familiar route and heading towards a visible landmark. We argue that this strategy switching is fundamentally important to navigation and that a deficit may contribute heavily to navigation impairments observed in aging.

According to the noradrenaline (NA) hypothesis, strategy switching is coordinated by the prefrontal cortex (PFC) and mediated by the locus coeruleus-noradrenaline (LCNA) system in response to changes in reward contingency, monitored by the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC; Aston-Jones and Cohen, 2005). The locus coeruleus (LC) operates in two modes; high phasic-low tonic, which promotes focused single task performance, and high tonic-low phasic, which promotes behavioral flexibility, such as strategy switching (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). The LC shows extensive degradation in aging (Mouton et al., 1994; Manaye et al., 1995; Grudzien et al., 2007) and NA shows signs of depletion or dysregulation (Luine et al., 1990; Li et al., 2001; Allard et al., 2011), suggesting that we may see an impairment in strategy switching in aging. Animal research has provided some support for the NA hypothesis. For example, Tait et al. (2007) tested rats on an attentional set shifting task that involves locating a reward based on one of two strategies. Following a lesion to the dorsal noradrenergic bundle (one of the LC's two main efferent fiber bundles), rats were impaired at switching between the two strategies compared to controls. Set shifting impairments have also been observed in aged mice (Young et al., 2010; Tanaka et al., 2011), monkeys (Moore et al., 2003; Hara et al., 2012), and humans (Ashendorf and McCaffrey, 2008; Gamboz et al., 2009),

demonstrating that aging and noradrenergic depletion at least have similar effects on strategy switching.

In navigation, numerous strategies are required in order to utilize a range of cues that are inconsistently available, as well as to operate on smaller and larger scales. These various strategies can be discriminated by reference frame, with some operating in relation to the body's changing orientation (egocentric), and others in relation to a static external coordinate system (allocentric). For example, using environmental cues to work out how to get to a known location relies on allocentric processing, while following a known route encoded as a series of turns depends on egocentric processing. Allocentric strategies have been demonstrated to depend on the hippocampus (O'Keefe, 1990; Hartley et al., 2003; Compton, 2004; Bohbot et al., 2007), while egocentric strategies have been associated with the caudate nucleus (Cook and Kesner, 1988; Iaria et al., 2003; Postle and D'Esposito, 2003). Hippocampal and caudal grey matter are negatively correlated, suggesting that these two areas operate in competition (Bohbot et al., 2007). It is thought that the PFC determines which of these parallel systems guides behavior (Doeller et al., 2008), supposedly as mediated by the ACC, OFC, and LCNA system, as above.

The plus maze task has been used extensively to study the use of allocentric and egocentric strategies in rats (Ragozzino, 2007; Rich and Shapiro, 2007). The task involves starting from one of two opposing arms of a plus-shaped maze and locating a reward at one of the two remaining arms. Which arm is rewarded depends on the current strategy (as well as the current start arm, which is pseudorandomised). Sometimes the subject is rewarded for finishing in a specific place, i.e., the east or west arm of the maze; at other times simply for a particular response, i.e., turning left or turning right. The task can therefore be used to study switches and reversals, much like the attentional set-shifting task, but in a navigational context. Several studies (Ragozzino et al., 1999; Rich and Shapiro, 2007; Young and Shapiro, 2009) have demonstrated impaired strategy switching, but unaffected reversals, following inactivation of regions of the medial PFC, which is both comparable to findings of studies using the attentional set shifting task, and consistent with the NA hypothesis. However, while some studies have used virtual mazes to assess spontaneous use of allocentric and egocentric strategies (Iaria et al., 2003; Bohbot et al., 2007), to our knowledge, there has not yet been any research into navigational strategy switching using human subjects.

We therefore set out to explore the effects of aging on navigational strategy switching in humans. We tested normal healthy young and old adults on a virtual version of the plus maze task. While the task is computerized, it is the same as the standard plus maze task in other respects, and still requires use of the same allocentric place-based and egocentric response-based strategies. We expected older people to exhibit a specific strategy switching impairment; performing worse than younger participants in blocks following a strategy switch, but not in those following a reversal, and not due to impaired learning of either strategy.

MATERIALS AND METHODS

PARTICIPANTS

Eighteen (10 female) young participants (20–29 years, mean 22.22 years) and 20 (11 female) old participants (60–84 years, mean 68.6 years) were recruited from existing databases of volunteers within the local communities of Edinburgh and Bournemouth. Most therefore had previous experience of participating in research. All participants had normal or corrected-to-normal vision and no known cognitive deficits or neurological disorders.

PROCEDURE

Participants provided information on their age, gender, and computer experience, before completing two computerized navigation tasks on a standard desktop computer with a 24″ widescreen monitor. In addition to age and gender information, participants were asked to rate their own experience of computers and of computer games on a nine-point scale from very inexperienced to very experienced. The first computer task, a spatial working memory task, was designed to assess memory for routes and places, as well as reward sensitivity. The second was the virtual plus maze task (VPM), designed to assess switching between different navigational strategies, such as egocentric response-based strategies and allocentric place-based strategies. Participants were made fully aware of these details of the experimental procedure, and all provided informed consent before participating. This study was approved by ethics committees at both the University of Edinburgh and Bournemouth University, and conformed to the Code of Ethics and Conduct of the British Psychological Society.

SPATIAL WORKING MEMORY TASK

This task served as a control task, designed to assess the working memory processes underlying performance at the main task; primarily place recall and route recall. Place recall trials were set in a virtual environment consisting of an open field surrounded by mountain scenery, with six identical landmarks arranged in a central circle. Participants were automatically moved to three of the six landmarks, returned to the origin and reoriented, then asked to revisit the same three landmarks in any order. Route recall trials were set in a grid like maze shrouded in fog to restrict visibility. Participants were first directed along a route through five junctions by arrows appearing at each one, then asked to retrace the same route without directions. An additional aspect of this task assessed sensitivity to the reward signal used in the main task. This signal would be the only feedback participants would receive in the main task, so it was important that they were able to monitor it. Throughout place and route encoding phases, the signal (a yellow ball) would sometimes appear at a landmark or junction. While revisiting the landmarks and retracing the routes, participants also had to indicate whether or not a ball had appeared at each location. The task included 10 place recall trials and 10 route recall trials, alternating between the two types.

VIRTUAL PLUS MAZE TASK

Our computerized adaptation of the plus maze task (**Figure 1**) allowed us to easily administer it to human subjects within a virtual environment. The environment consisted of a grass-textured ground plane, surrounded by continuous mountain scenery, with a central plus maze composed of curbed paths and transparent walls. The continuous mountain scenery provided visual cues from which participants could infer their orientation, without including localized landmarks that could be used as beacons. In

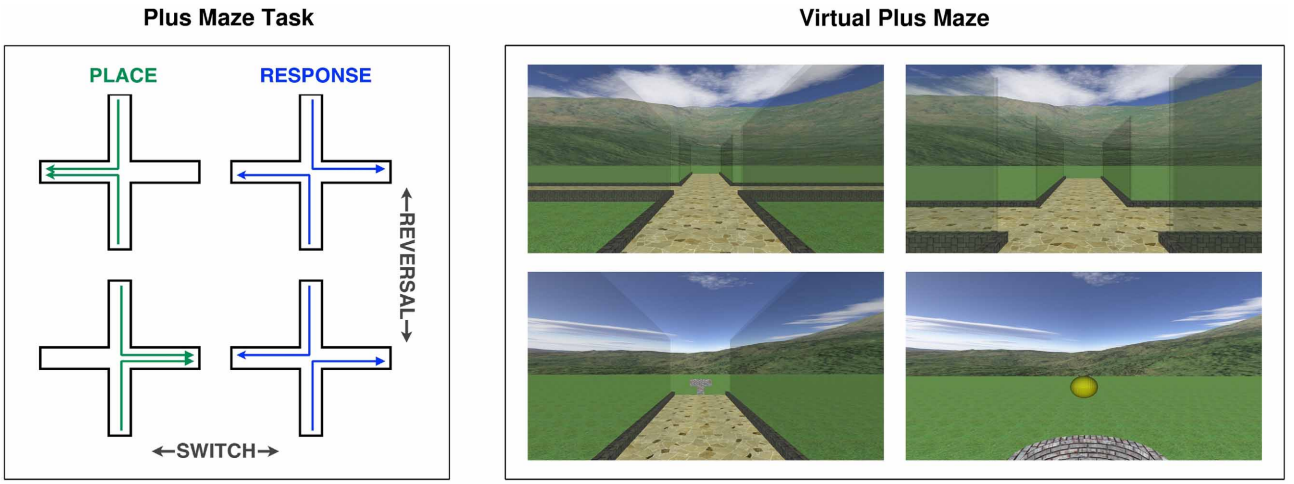

FIGURE 1 | Left: Diagrammatic representation of the plus maze task, illustrating place and response strategies, and switch and reversal change types. **Right:** Screen images captured during the virtual plus maze task, at the start point, at the junction before turning, at the junction after turning and at the goal (showing a reward).

each trial, participants started from one of two opposing start arms (in a pseudorandomised order), approached the central junction, and decided within 3 s whether to turn left or right in order to find a reward at one of the other two goal arms. A yellow ball emerged from the well at the end of the goal arm as a reward signal if the correct choice was made. Participants were rewarded either for going to the correct place (i.e., east or west, regardless of required response), or for making the correct response (i.e., left or right, regardless of heading). Between blocks of 20 trials, either a switch, a reversal or no change occurred. Switches changed the rewarded strategy from place to response, or vice versa. Reversals retained the same strategy, but changed the rewarded place or response, e.g., from east to west, or from left to right. These changes were made less predictable by the inclusion of no changes between some blocks. Participants completed a total of 320 trials, incorporating five switches and five reversals. This included three switches in one direction and two in the other, as well as three reversals for one strategy and two for the other, depending on the starting strategy, which was alternated and counterbalanced within each age group.

DATA ANALYSIS

Data analysis was performed in Matlab (Mathworks, Natick, MA). Computer experience information was combined to produce a single score. Spatial working memory task data were reduced to three scores for place recall (total correct places visited), route recall (total correct turns made), and reward sensitivity (total rewards remembered). VPM performance was assessed in terms of the number of correct trials, the number of blocks for which the strategy was learned, and the number of trials for which the learned strategy was stable. Data from blocks following no change were merged with data for the previous block. One young female participant was excluded as an outlier, as she performed more than two standard deviations below the group mean in terms of overall number of trials correct. We then used mixed model ANOVAs and t-tests to assess differences between age groups in numbers of trials correct, blocks learned and stable trials. p-values were adjusted correct for multiple comparisons according to the Bonferroni method. We also performed stepwise regression analyses to assess the contribution of age, gender, computer use, and spatial working memory task performance to measures of VPM performance.

Learning was analyzed using a Bayesian estimation procedure developed by Smith and colleagues (Smith et al., 2004, 2005, 2007), together with WinBUGs (Lunn et al., 2000) and the "matbugs" Matlab function. This approach can be used to estimate, at each time point throughout a series of trials, the likelihood of responses to all subsequent trials being correct, based on observed performance data. The point at which the lower 95% confidence interval of this estimation first exceeds and remains above the chance probability of a correct response for each individual trial (50% in this experiment) corresponds to acquisition of the reward contingency. We used this to identify whether or not the strategy was learned for each block and, if so, for how many trials the learned strategy was stable, i.e., the number of trials after the point of acquisition.

RESULTS

Older participants performed worse at the VPM in terms of overall performance, measured as the total number of trials correct ($t_{35} = 3.052$, $p = 0.002$), strategy learning, in terms of the total number of blocks learned ($t_{35} = 3.301$, $p = 0.001$), and learning speed, as indicated by the number of trials for which the learned strategy remained stable ($t_{35} = 3.107$, $p = 0.002$; **Figure 2**). They also reported a significantly lower level of computer experience ($t_{33} = 3.705$, $p < 0.001$) and performed worse at the spatial working memory task in terms of place recall ($t_{35} = 4.701$, $p < 0.001$) and reward sensitivity ($t_{35} = 3.596$, $p < 0.001$), although not route recall ($t_{35} = 0.381$, $p = 0.353$). We performed stepwise

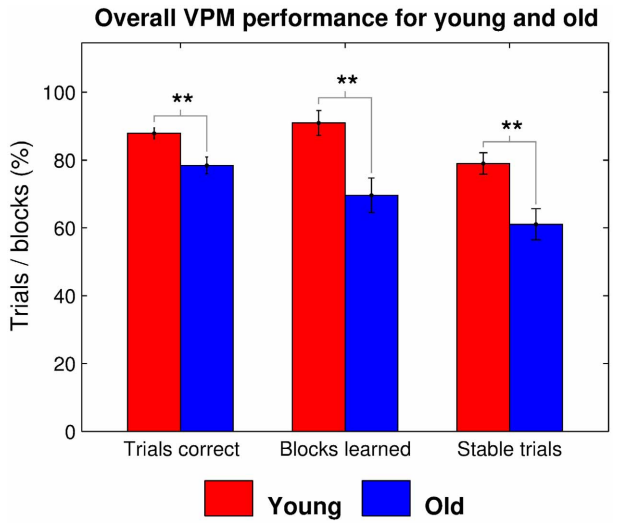

FIGURE 2 | Overall virtual plus maze task performance, as measured by the mean percentage of trials correct, blocks learned, and stable trials for young (red) and old (blue) participants. Significant group differences are indicated at the *0.05, **0.01, and ***0.001 levels.

Table 1 | Results of stepwise regression analysis predicting trials correct, with significant predictors (age group) highlighted in blue.

Trials correct				
Predictor	**β**	**SE**	**In**	***p***
Age group	−9.673	3.089	Yes	0.004
Gender	3.921	3.126	No	0.219
Computer use	−0.391	0.742	No	0.602
Place recall	−0.009	0.385	No	0.981
Route recall	0.358	0.239	No	0.144
Reward sensitivity	0.510	0.301	No	0.100

Table 2 | Results of stepwise regression analysis predicting blocks learned, with significant predictors (age group) highlighted in blue.

Blocks learned				
Predictor	**β**	**SE**	**In**	***p***
Age group	−22.222	6.521	Yes	0.002
Gender	7.460	6.628	No	0.269
Computer use	−1.168	1.560	No	0.460
Place recall	−0.523	0.807	No	0.521
Route recall	0.801	0.503	No	0.121
Reward sensitivity	0.897	0.644	No	0.174

Table 3 | Results of stepwise regression analysis predicting stable trials, with significant predictors (age group) highlighted in blue.

Stable trials				
Predictor	**β**	**SE**	**In**	***p***
Age group	−18.295	5.738	Yes	0.003
Gender	7.032	5.814	No	0.235
Computer use	−0.558	1.381	No	0.689
Place recall	−0.241	0.714	No	0.738
Route recall	0.731	0.441	No	0.107
Reward sensitivity	0.981	0.557	No	0.088

regression analyses to check for factors that predicted VPM performance, which confirmed that age was a significant predictor in terms of overall trials correct ($\beta = 9.673$, $p = 0.004$), blocks learned ($\beta = 22.222$, $p = 0.002$), and stable trials ($\beta = 18.295$, $p = 0.003$). However, none of the potential control variables (gender, computer use, place recall, route recall, and reward sensitivity) were retained in the models as significant predictors of any of the measures of VPM performance (**Tables 1–3**). Further stepwise regression analyses for each age group separately (excluding age as a predictor) maintained that none of the potential control variables were significant predictors for any measure of VPM performance. These variables were therefore not considered in further analyses.

To explore the root of the age-related deficit in VPM performance, we split the data by block type for further analyses. We first used One-Way repeated measures ANOVAs to check for learning effects across blocks of each strategy type for each age group, but found no main effect of block order on performance (young place: $F_{(85,\ 4)} = 0.790$, $p = 0.535$; young response: $F_{(85,\ 4)} = 0.401$, $p = 0.808$; old place: $F_{(94,\ 4)} = 0.828$, $p = 0.511$; and old response: $F_{(94,\ 4)} = 0.826$, $p = 0.512$), allowing us to average performance across blocks of the same type. We then performed Two-Way mixed ANOVAs with age group as a between-groups factor and block strategy as a within-subjects factor, assigning data from place and response blocks to separate conditions. These demonstrated a significant main effect of both age (trials correct: $F_{(35,\ 1)} = 9.356$, $p = 0.004$; blocks learned: $F_{(35,\ 1)} = 11.929$, $p = 0.001$; and stable trials: $F_{(35,\ 1)} = 9.689$, $p = 0.004$) and strategy (trials correct: $F_{(35,\ 1)} = 6.450$, $p = 0.016$; blocks learned: $F_{(35,\ 1)} = 10.678$, $p = 0.002$; and stable trials: $F_{(35,\ 1)} = 7.149$, $p = 0.011$) on all three measures of VPM performance, as well as significant interactions between the two (trials correct: $F_{(35,\ 1)} = 6.709$, $p = 0.014$; blocks learned: $F_{(35,\ 1)} = 8.133$, $p = 0.007$; and stable trials: $F_{(35,\ 1)} = 7.293$, $p = 0.011$). *Post-hoc* tests revealed that older people performed worse specifically during place blocks (trials correct: $t_{35} = 3.189$, $p_B = 0.003$; blocks learned: $t_{35} = 3.485$, $p_B = 0.002$; and stable trials: $t_{35} = 3.287$, $p_B = 0.002$; **Figure 3**), accounting for the main effects of age and strategy, as well as for the interaction between them. This seems to suggest that older people may exhibit an allocentric strategy deficit.

However, we then performed further ANOVAs with change type as the within-subjects factor, including data for blocks following switches and blocks following reversals in separate conditions. Data from blocks following unlearned blocks had to be excluded, as, even if that block was learned, it may not have necessitated a strategy switch or reversal. Data from the first block was also excluded as it of course preceded all changes. These gave similar results, again demonstrating a

significant main effect of age (trials correct: $F_{(35,\ 1)} = 8.083$, $p = 0.007$; blocks learned: $F_{(35,\ 1)} = 9.790$, $p = 0.004$; and stable trials: $F_{(35,\ 1)} = 8.441$, $p = 0.006$), and also a significant main effect of change type (trials correct: $F_{(35,\ 1)} = 23.112$, $p < 0.001$; blocks learned: $F_{(35,\ 1)} = 20.976$, $p < 0.001$; and stable trials: $F_{(35,\ 1)} = 26.915$, $p < 0.001$) and a significant age by change type interaction (trials correct: $F_{(35,\ 1)} = 5.074$, $p = 0.031$; blocks learned: $F_{(35,\ 1)} = 7.277$, $p = 0.011$; and stable trials: $F_{(35,\ 1)} = 6.638$, $p = 0.014$) for all three dependent variables. *Post-hoc* tests revealed that older people performed worse specifically for blocks following strategy switches (trials correct: $t_{35} = 2.667$, $p_B = 0.012$; blocks learned: $t_{35} = 3.043$, $p_B = 0.004$; and stable trials: $t_{35} = 2.878$, $p_B = 0.007$; **Figure 4**), accounting for the effects of age and change type and the interaction between them. This seems to suggest that older people are impaired at strategy switching, rather than simply at employing allocentric strategies.

Taken together, these results suggest that either older people exhibit two separate general deficits in allocentric strategy use and strategy switching, which both contribute to impaired VPM performance, or they exhibit a more specific deficit in switching to an allocentric strategy. We assessed these two hypotheses by separating the data into four block types; those following a switch to the place strategy (S2P), those following a switch to response (S2R), those after a reversal of place (RP) and those after a reversal of response (RR). Further mixed ANOVAs with block type as the within-subjects factor revealed a significant main effect of age (trials correct: $F_{(35,\ 1)} = 8.949$, $p = 0.005$; blocks learned: $F_{(35,\ 3)} = 9.486$, $p = 0.004$; and stable trials: $F_{(35,\ 3)} = 8.177$, $p = 0.007$) and block type (trials

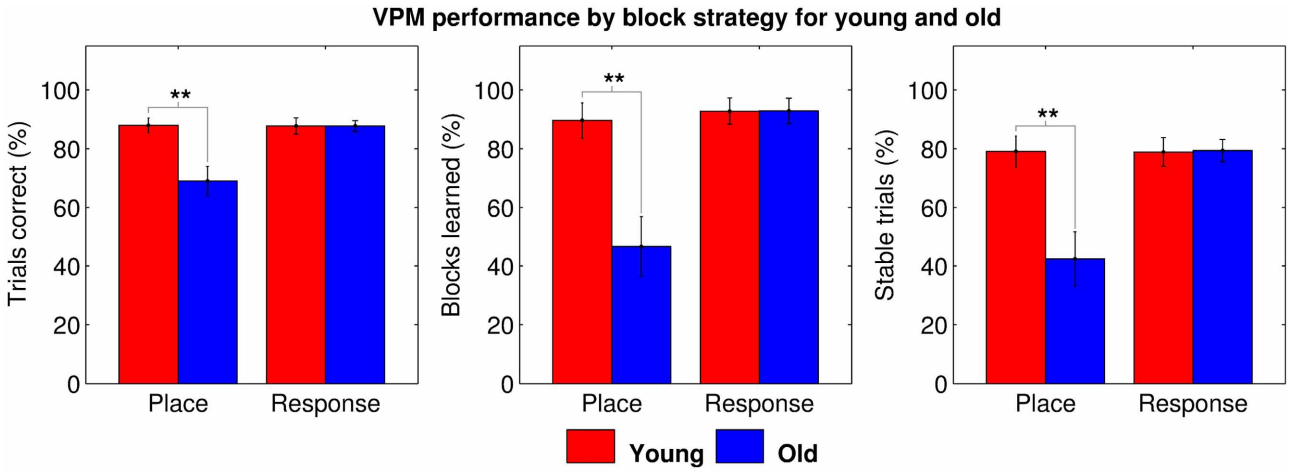

FIGURE 3 | VPM performance in terms of trials correct (left), blocks learned (middle), and stable trials (right) during place and response blocks for young (red) and old (blue) participants. Significant group differences are indicated at the *0.05, **0.01, and ***0.001 levels following Bonferroni correction.

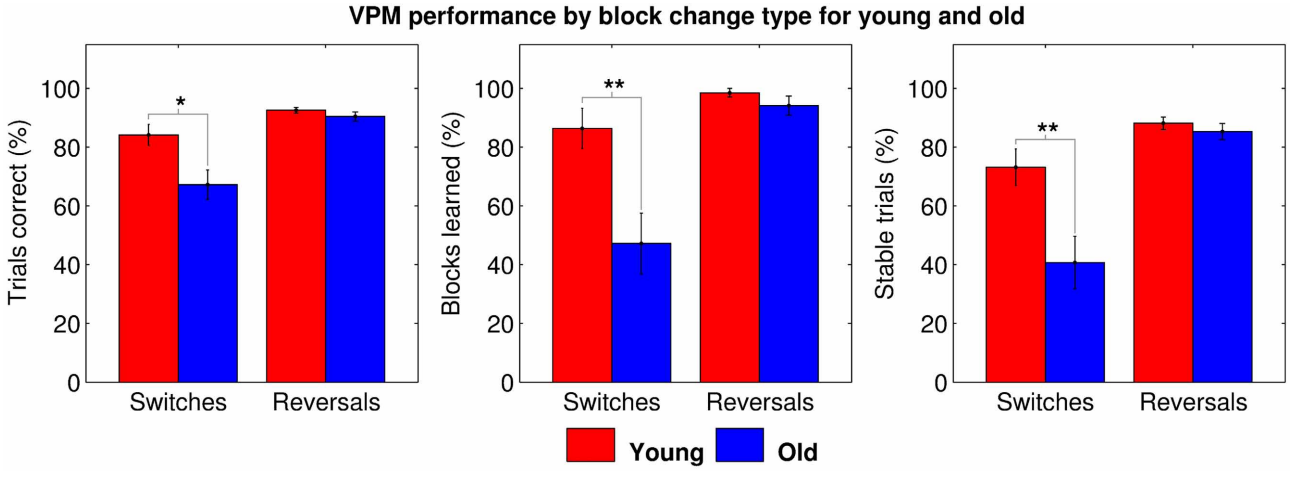

FIGURE 4 | VPM performance in terms of trials correct (left), blocks learned (middle), and stable trials (right) during blocks following switches and reversals for young (red) and old (blue) participants, excluding data from first blocks and blocks following unlearned blocks. Significant group differences are indicated at the *0.05, **0.01, and ***0.001 levels following Bonferroni correction.

correct: $F_{(35,\ 1)} = 9.762$, $p < 0.001$; blocks learned: $F_{(35,\ 3)} = 9.927$, $p < 0.001$; and stable trials: $F_{(35,\ 3)} = 9.755$, $p < 0.001$) as well as a significant interaction between the two (trials correct: $F_{(105,\ 3)} = 5.702$, $p = 0.001$; blocks learned: $F_{(105,\ 3)} = 6.773$, $p < 0.001$; and stable trials: $F_{(105,\ 3)} = 5.570$, $p = 0.001$). *Post-hoc* tests clarified that this was due to a more specific deficit in switching to place blocks (trials correct: $t_{33} = 2.895$, $p_B = 0.013$; blocks learned: $t_{33} = 3.634$, $p_B = 0.002$; and stable trials: $t_{33} = 3.192$, $p_B = 0.006$; **Figure 5**) among the older participants.

In an effort to understand why older participants failed to learn the place strategy following a switch, we explored the use of alternative strategies during unlearned blocks. For this analysis we simply associated each block with a particular strategy-direction combination if the participant responded in accordance with it significantly more than expected by chance ($p < 0.001$). As shown in **Figure 6**, while older participants often simply did not acquire any strategy, for the majority of the time they employed an incorrect strategy. Interestingly, the older participants used an incorrect place strategy just as often as an incorrect response strategy, providing evidence that they were able to use a place strategy just as well, despite the deficit in switching to this strategy (switch-to-place deficit). The older group also exhibited perseverative errors (continuing to use the strategy from the block preceding a change) in less than one third of blocks in which they used an incorrect strategy, suggesting that, in most cases, failure to learn the correct strategy was not simply due to failure to detect a change in reward contingency. There was very little incidence of regressive errors (changing back to the strategy used before the block preceding a change). Where other types of error were made, older participants again used both incorrect place and response strategies, suggesting that they were not simply reverting to a preferred response strategy.

We also assessed response times, but while the older participants generally took significantly longer to respond ($t_{35} = 3.159$, $p = 0.003$), this difference was consistent across all block types (switch to place: $t_{35} = 2.721$, $p_B = 0.040$; switch to response: $t_{35} = 2.984$, $p_B = 0.021$; RP: $t_{35} = 3.315$, $p_B = 0.009$; and RR: $t_{35} = 2.577$, $p_B = 0.057$). This suggests that the difference in response time was not related to differences in overall performance or the switch-to-place deficit reported above. A difference in response times could have affected performance due to the limited time (3 s) that participants had to respond, but very few participants from either group ever took longer than this to respond, and there was no significant difference between groups in the number of trials to which a response was not provided in time ($t_{35} = 0.920$, $p = 0.364$). Interestingly, response times did not increase significantly following a switch or reversal ($t_{35} = 0.971$, $p = 0.335$).

DISCUSSION

We demonstrated aging-impaired navigation using a VPM, with older participants responding correctly for significantly fewer trials, stably acquiring the correct strategy for significantly fewer blocks, and maintaining a stable strategy for significantly fewer trials. As expected, this impairment was related to decreased ability—as measured by numbers of trials correct, blocks learned and stable trials—to switch between navigational strategies, despite intact ability to perform reversals within strategies. However, further investigation revealed that this deficit was more specific than expected, applying only to switching in one direction; to the place strategy. There was a significant age difference in trials correct, blocks learned, and stable trials for place blocks following a switch, but none for post-switch response blocks, or for blocks of either strategy following a reversal. This specific effect also produced an apparent age difference in performance during place blocks but not response blocks, in contrast to our original hypothesis. We also explored the behavior of older participants

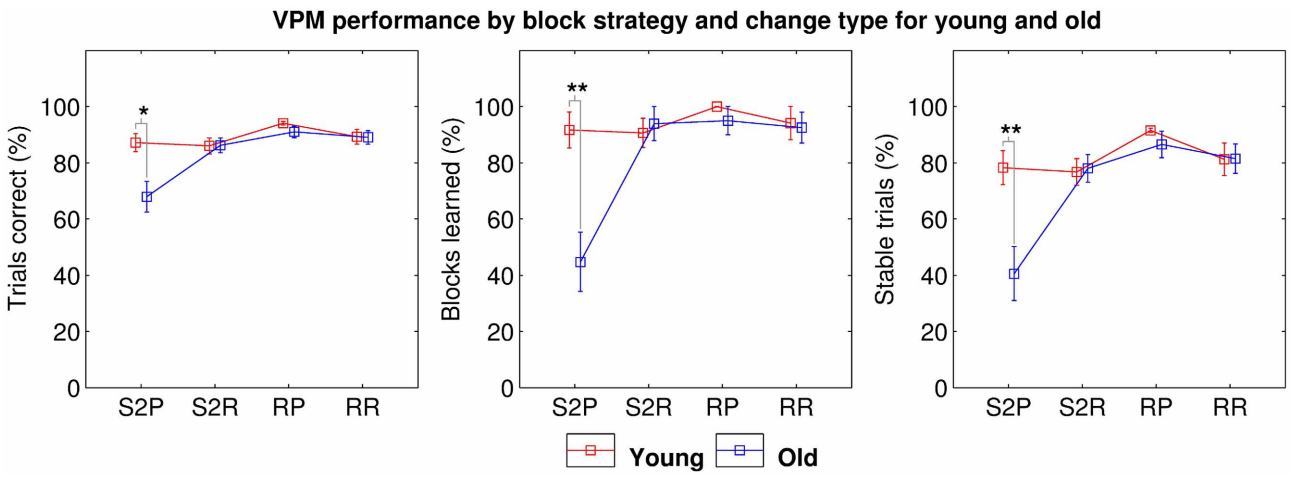

FIGURE 5 | VPM performance in terms of trials correct (left), blocks learned (middle), and stable trials (right) during blocks following switches to the place strategy (S2P), switches to the response strategy (S2R), reversals of place (RP), and reversals of response (RR) for young (red) and old (blue) participants, excluding data from first blocks and blocks following unlearned blocks. Significant differences are indicated at the *0.05, **0.01, and ***0.001 levels following Bonferroni correction.

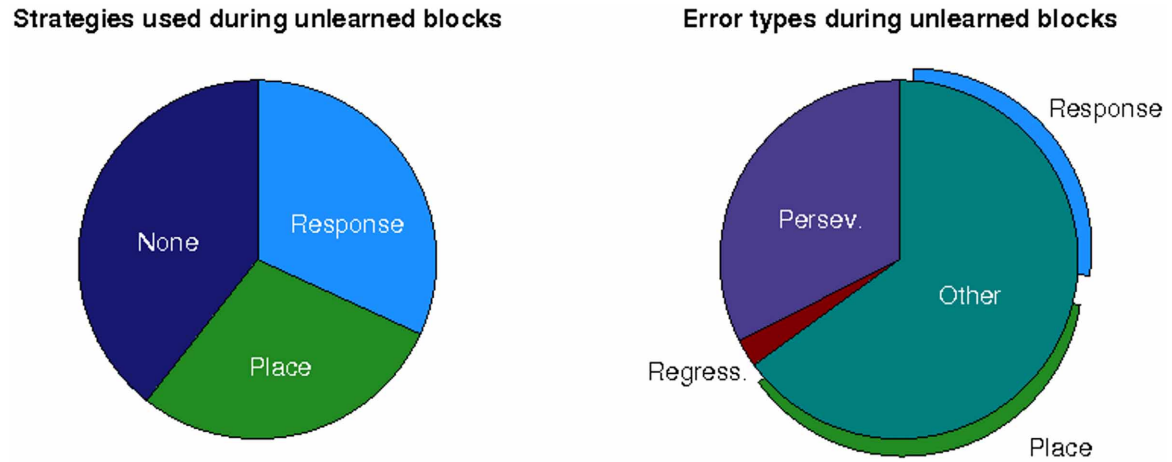

FIGURE 6 | Left: Strategies used during unlearned blocks as a proportion of all unlearned blocks for old participants. **Right:** Error types made during unlearned blocks as a proportion of all unlearned blocks in which an incorrect strategy was used for old participants.

during unlearned blocks, finding that while they often failed to acquire any strategy, they more often used an incorrect strategy, and that this was not usually attributable to perseverative or regressive error types.

Our initial results appeared to provide evidence of an age-related strategy switching deficit, as hypothesized and as found previously using set-shifting tasks (Moore et al., 2003; Gamboz et al., 2009; Young et al., 2010). Such a deficit can be interpreted in terms of the NA hypothesis of strategy switching (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005), as LCNA dysfunction is observed in aging (Mouton et al., 1994; Li et al., 2001; Grudzien et al., 2007) and has been shown to impair strategy switching (Tait et al., 2007). During unlearned blocks, older participants did not usually exhibit perseverative errors, suggesting that any switching deficit would result from a failure of the LCNA system and PFC to engage a new strategy, rather than a failure of the ACC/OFC to detect a change in reward, or of the LCNA system to disengage the old strategy.

However, while we hypothesized a general strategy switching deficit, we found that the older participants did not exhibit an impairment in switching from the place to the response strategy. We also found an age difference in performance during place blocks, which may have indicated an allocentric processing deficit, as demonstrated previously in older animals (Frick et al., 1995; Kikusui et al., 1999; Begega et al., 2001). But similarly, this did not apply to place blocks following a reversal, and therefore did not suggest a general allocentric processing deficit. Instead, we found that these effects could both be attributed to a single specific impairment in switching to the place strategy. We believe this is the first study to identify this specific impairment, but we propose that previous findings interpreted as evidence of a general strategy switching deficit may actually relate to this more specific deficit. Furthermore, impaired switching to allocentric processing is likely to affect navigation in general, and may account for previous findings of age-related decline in allocentric navigation performance.

A strategy switching deficit could be attributed to LCNA or PFC dysfunction (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005), whereas an allocentric processing deficit would most likely be attributed to hippocampal atrophy (Driscoll et al., 2003; Du et al., 2003, 2006). However, the cohort of older participants used in this study appear to have retained normal functionality of the areas of PFC and hippocampus responsible for co-ordinating switching and allocentric navigation, respectively. The specific switch-to-place deficit observed may instead stem from a functional difference somewhere between these two systems in the network involved in guiding navigation. We speculate that the interaction between hippocampus and PFC may be compromised in the older participants. In this case, when a response strategy is no longer rewarded, a switch would still be initiated by the LCNA system and the hippocampal place strategy would still be available to switch to, but the PFC would fail to select the place strategy as the best to use, perhaps due to reduced weighting of inputs from the hippocampus. If the weighting of caudal inputs is retained, then switches to response should be unaffected. Similarly, once a place strategy has been selected, although this will be more difficult, use of the strategy and performance of reversals should also remain unimpaired. There is some existing evidence of a change in the functional connectivity between the hippocampus and PFC in aging and dementia (Grady et al., 2003; Wang et al., 2006; Bai et al., 2009).

Reduced hippocampal-prefrontal connectivity could also account for other aspects of navigational aging, such as a preference among older people for egocentric strategies (Rodgers et al., 2012; Wiener et al., 2012). We recently demonstrated that this preference persists even when an allocentric strategy would be more beneficial to task performance (Wiener et al., submitted). This may result from older people's inability to switch to an allocentric strategy, due in turn to reduced hippocampal-prefrontal

connectivity. Alternatively, reduced hippocampal-prefrontal connectivity could effect this strategy preference directly. In this case, the egocentric preference may contribute to the switch-to-place deficit. In the present study, older participants may have found it easier to switch to the response strategy due to their egocentric strategy preference, thus masking the effects of a more general switching deficit on their switch-to-response performance. Unfortunately, this behavioral data does not allow us to easily discern whether the effects were due solely to an age difference in functional hippocampus-PFC connectivity underlying the switch-to-place deficit, nor whether there was additional dysregulation of the LCNA system, corresponding to a more general deficit in strategy switching in combination with an egocentric strategy preference. Further investigation using neuroimaging is necessary to confirm the functional, morphological, or structural changes responsible for the behavioral age differences reported here.

In summary, we have demonstrated a specific age-related deficit in switching to an allocentric navigational strategy, while both switching to an egocentric strategy and reversals within strategies were unaffected. This deficit is unlikely to result from diminished allocentric processing functionality of the hippocampus, as older participants were still able to use a place strategy, and sometimes did so even when incorrect. It is also unlikely to stem from an impairment in reward monitoring in the ACC or OFC, as most errors made by older participants were not perseverative. Instead, we propose that the deficit corresponds to a failure to engage the place strategy due to decreased functional connectivity between the hippocampus and PFC. Dysregulation in the LCNA system may also contribute to this deficit, either in combination with a preference for egocentric strategies, or simply because the hippocampus-PFC connection could be affected by noradrenergic input from LC. Whatever the underlying cause, the specific switch-to-place deficit may explain more general impairments in navigational strategy switching and allocentric processing that have been observed previously, and is likely to contribute to the age-related decline of navigation ability in general.

ACKNOWLEDGMENTS

This study was funded by the University of Edinburgh, Bournemouth University, and the Biotechnology and Biological Sciences Research Council. Thanks also to Richard West and Cathy Spain for help with data collection, and to Anne Smith for assistance with running the learning analysis.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 June 2012; accepted: 14 October 2012; published online: 01 November 2012.

*Citation: Harris MA, Wiener JM and Wolbers T (2012) Aging specifically impairs switching to an allocentric navigational strategy. Front. Ag. Neurosci. **4**:29. doi: 10.3389/fnagi.2012.00029*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 September 2012
doi: 10.3389/fnagi.2012.00026

Age differences in virtual environment and real world path integration

Diane E. Adamo[1,2], Emily M. Briceño[3], Joseph A. Sindone[4], Neil B. Alexander[5] and Scott D. Moffat[6]*

[1] Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA
[2] Institute of Gerontology, Wayne State University, Detroit, MI, USA
[3] Department of Psychology, Wayne State University, Detroit, MI, USA
[4] Department of Linguistics, University of Michigan, Ann Arbor, MI, USA
[5] Mobility Research Center, Geriatrics Center and Division of Geriatric Medicine, University of Michigan Hospitals and Veterans Affairs Ann Arbor Health Care System Geriatric Research Education and Clinical Center, Ann Arbor, MI, USA
[6] School of Psychology, Georgia Institute of Technology, Atlanta, GA, USA

Edited by:
Thomas Wolbers, German Center for Neurodegenerative Diseases (DZNE), Germany

Reviewed by:
Mark May, Helmut-Schmidt University Hamburg, Germany
Mathew A. Harris, University of Edinburgh, UK

***Correspondence:**
Scott D. Moffat, School of Psychology, Georgia Institute of Technology, J. S. Coon Bldg., 654 Cherry Street, Atlanta, GA 30332-0170, USA.
e-mail: scott.moffat@psych.gatech.edu

Accurate path integration (PI) requires the integration of visual, proprioceptive, and vestibular self-motion cues and age effects associated with alterations in processing information from these systems may contribute to declines in PI abilities. The present study investigated age-related differences in PI in conditions that varied as a function of available sources of sensory information. Twenty-two healthy, young (23.8 ± 3.0 years) and 16 older (70.1 ± 6.4 years) adults participated in distance reproduction and triangle completion tasks (TCTs) performed in a virtual environment (VE) and two "real world" conditions: guided walking and wheelchair propulsion. For walking and wheelchair propulsion conditions, participants wore a blindfold and wore noise-blocking headphones and were guided through the workspace by the experimenter. For the VE condition, participants viewed self-motion information on a computer monitor and used a joystick to navigate through the environment. For TCTs, older compared to younger individuals showed greater errors in rotation estimations performed in the wheelchair condition, and for rotation and distance estimations in the VE condition. Distance reproduction tasks (DRTs), in contrast, did not show any age effects. These findings demonstrate that age differences in PI vary as a function of the available sources of information and by the complexity of outbound pathway.

Keywords: aging, Alzheimer's disease, hippocampus, navigation, path integration, spatial memory

INTRODUCTION

An important aspect of spatial navigation is path integration (PI) (Mittelstaedt and Mittelstaedt, 1982; Cheng and Spetch, 1998), which refers to the ability to monitor one's position in space using self-motion cues derived from visual (linear and radial optic flow), vestibular (translational and rotational accelerations), and/or proprioception (feedback from muscles, tendons, and joints). Optic flow refers to the processing of the flow of visual information resulting from movement of the observer. Decline in the ability to process optic flow has been linked with declines in navigation abilities observed with early onset of Alzheimer's disease (deIpolyi et al., 2007). Vestibular cues derived from sensory receptors in the middle ear (utricle, saccule, and semicircular canals) detect differences in linear and angular accelerations. Detecting changes in the speed of translation (distance-specific) and rotation (direction-specific relative to global spatial coordinates) contribute to updating spatial information used in PI tasks. Support for the importance of vestibular information in PI is evidenced by the observation that labyrinthine-defective human subjects have difficulty estimating and reproducing the length of a path or a previously seen target (Glasauer et al., 1994, 1999). Proprioception provides information about body and limb position awareness and is used to mediate one's conscious perception of movement (Goodwin et al., 1972; McCloskey, 1978; Gandevia et al., 1992) and encode body movements in space (Chance et al., 1998; Mittelstaedt and Mittelstaedt, 2001). Thus, these primary sensory systems all contribute significantly to the ability to navigate one's environment.

Studies on ants (Cheng et al., 2009), bees (Frisch, 1967), and, particularly, rodents (Mittelstaedt and Mittelstaedt, 1982; Etienne et al., 1988) show that when eliminating visual and olfactory cues (Etienne et al., 1986) animals are able to use PI effectively (Mittelstaedt and Mittelstaedt, 1982; Jeffery et al., 1997). Although sensory-specific contributions to PI vary within species, bees rely on optic flow (Srinivasan et al., 2000) and ants determine distance through proprioceptors (Wohlgemuth et al., 2001). In rats, recordings from anterior thalamic head-direction cells show that vestibular and visual movement cues, along with motor efferent information (Zugaro et al., 2001) work interactively to determine the directional frame of reference during PI tasks (Sharp et al., 1995; Blair and Sharp, 1996).

Although specific procedures employed to evaluate *human* PI vary, paradigms typically restrict participants to a subset of self-motion cues (visual, vestibular, and proprioceptive) in order to

evaluate the relative contribution of sensory input (Loomis et al., 1993; Chance et al., 1998; Philbeck et al., 2008). To restrict individuals to proprioceptive and vestibular information, participants typically wear a blindfold and noise-blocking headphones and are then required to reproduce movements through which they were transported. Individuals may be moved along a single linear distance and be asked to return to the origin by reproducing the distance they traveled by moving in the opposite direction. In contrast, triangle completion tasks (TCTs) are more complicated in that participants may be moved along two legs of a triangle and then when reaching the end of the second leg of the triangle, must rotate and return to the origin without assistance. In this task, spatial components associated with angles turned and distances traveled must be successfully integrated in order to approximate the return to the origin.

Healthy young adults are fairly accurate when reproducing distances and angular rotations (Mittelstaedt and Mittelstaedt, 1982, 2001; Israel and Berthoz, 1989; Glasauer et al., 1994; Israel et al., 1995; Ivanenko et al., 1997; Marlinsky, 1999). In addition, Wiener et al. (2011) showed that head orientation assists with deriving a homing vector for locomotion tasks performed in the absence of visual and auditory information. However, when required to combine linear and rotational displacements simultaneously (as in TCTs), healthy young adults demonstrate greater difficulty with the task, with errors mainly driven by the rotation component of the movement (Loomis et al., 1993; Marlinsky, 1999). Further, the contribution of motor-efferent signals derived from self-movements cannot be ignored as a source of information contributing to PI abilities (Mittelstaedt and Mittelstaedt, 2001).

Despite numerous demonstrations of age-related declines in navigation in both human (Moffat and Resnick, 2002; Driscoll et al., 2005; Cushman et al., 2008; Rodgers et al., 2012) and nonhuman (Ingram, 1988; McLay et al., 1999) species, few studies have investigated possible age differences in PI. Allen et al. (2004) found that older adults performed similarly to young adults when returning to the origin of a triangle under guided walking conditions. However, when performing this same task following passive conveyance in a wheelchair, older individuals showed greater errors than young individuals, suggesting that performance is related to the amount of sensory information available. That is, age differences are minimized when both proprioceptive and vestibular perceptual signals are available. In a study designed to examine age-differences in visual PI, Mahmood et al. (2009) found that older compared to younger adults had greater difficulty in a TCT presented on a computer. Similar age effects in PI were observed by Harris and Wolbers (2012) using a virtual environment (VE).

Although age-related declines in PI have been demonstrated in one real-world and two VE studies, the extent to which each of the sources of sensory information contribute to these differences is not known as no study has investigated all three sensory systems in the same participants. This is critical as each sensory system known to contribute to PI, shows some age-related decline (Adamo et al., 2007, 2009; Horning and Gorman, 2007; Kulmala et al., 2008). Understanding the contribution of sensory-specific information to PI abilities may contribute to improving interventions to offset age-associated declines in wayfinding abilities that rely on the integration of sensory specific information (Loomis et al., 1993; Chance et al., 1998; Philbeck et al., 2008) and cognitive functions (Davis et al., 2008). Therefore, the present study investigated the relative contribution of three sources of sensory information to age-related differences in PI. The contribution of various sources of sensory information to PI was investigated by providing conditions that reduced a source of sensory information. For blindfolded/auditory blocking walking conditions self-motion cues were derived primarily from proprioceptive and vestibular cues. Motor efferent information is also available. For blindfolded/auditory blocking wheelchair propulsion conditions self-motion cues were primarily derived from vestibular cues since they were seated in a wheelchair and only performed active movements when operating the joystick during return paths. During VE conditions, self-motion cues were derived from optic flow and there were no visual landmark or cues available. Passive viewing was completed before individuals used a joystick to complete return paths. For outbound paths, sensory information was specific to each condition. In the wheelchair and VE conditions return paths required the use of a joystick to complete task requirements. The focus of this study investigated PI abilities derived specifically from self-movement cues.

METHODS

Thirty-eight, right handed, young ($n = 22$, 10 female, mean age $= 23.8 \pm 3.0$ years) and older ($n = 16$, 11 female, mean age $= 70.1 \pm 6.4$ years) adults participated in this study. Participants were free from any neurological or musculoskeletal conditions that may have impaired performance and scored >28/30 on the Mini Mental State Exam (MMSE) (Folstein et al., 1975). Visual acuity was 20/40 or higher for all individuals. Participants were recruited from the Metropolitan Detroit/Ann Arbor area and Wayne State University. Informed consent approved by the Institutional Review Board at the University of Michigan and the Human Investigation Committee at Wayne State University was completed before each testing session.

SCREENING TOOLS AND ASSESSMENTS

Vision and mobility assessments were administered to all participants. Tests for contrast sensitivity (Mars Letter Contrast Sensitivity Test) and color vision (Ishihara Color Plates Test) ensured that any potential visual deficits would not interfere with their ability to perform the VE condition. The Timed Up and Go task (Podsiadlo and Richardson, 1991) assessed safe walking ability. To determine whether the participants experienced any symptoms of motion sickness following performance of the tasks in the VE, the 16-item Nausea Symptom Questionnaire was administered.

EXPERIMENTAL SET-UP

Two real world conditions and one VE condition were used to assess PI abilities. The real world conditions consisted of guided walking and wheelchair propulsion and took place in a human research laboratory that was 12.2×9.1 m. For both real world conditions, participants wore a halo structure on their head. This

consisted of a rigid plastic structure that was placed on the head in a position parallel to the ground. The halo was embedded with eight equally distributed reflective markers (Light Emitting Diodes, LEDs) that were connected with a thin cable and then to a transmitter. The transmitter powered the reflective markers, and the position of the reflective markers embedded in the halo was recorded by four Optotrak Certus™ position sensors (cameras) placed in the testing volume. The reflective markers tracked whole body movements.

For the walking condition, a gait belt worn by the participant and lightly grasped by the experimenter was used to steer the participants through the distances traveled and angles turned during the walking task. Participants also wore noise-reducing earphones and a blindfold to suppress auditory and visual information. Comfortable walking shoes were worn.

For the wheelchair condition, participants were comfortably seated in an IMC Heartway Rumba S HP with a Dynamic DL 5.2i armrest control unit mounted on the right side of the chair. Individuals moved a joystick device with their right hand to execute forward, backward, and turning movements while seated in the chair.

The VE condition was administered using a modified version of Unreal Tournament 2003 and the software package Unreal Editor 3.0 (Epic Games, Inc.). In a dimly lit room, participants were seated 23″ away from an 18″ flat screen LCD monitor. Seat height was adjusted so that the eyes were level with the midpoint of the computer monitor. A Thrustmaster Top Gun Fox 2 Pro joystick mounted on top of a 27 5/8th in. platform was placed on the right side of the individual. The VE condition consisted of passively viewing a movement trajectory on a computer monitor, then maneuvering a joystick when responding to the requirements of the active portion of the task (see below).

EXPERIMENTAL PROCEDURES

Following completion of screening tools, participants performed PI tasks in the following order: walking, wheelchair propulsion, and VE. The VE was presented last because of concerns that motion sickness or dizziness induced by VE navigation may affect performance on the real world tasks and may increase risk for falls in the blindfolded walking condition. For each condition, two tasks were performed that consisted of: (1) rotating and returning to the origin of a triangle and (2) reproducing a linear distance traveled.

REAL WORLD-TRIANGLE COMPLETION AND DISTANCE REPRODUCTION TASKS

The TCT involved passive motion of two linear distances separated by one angular rotation. For real-world walking, participants were guided along the first leg of a triangle and brought to a complete stop. The experimenter then rotated and guided participants through the second leg of the triangle. After stopping at the end of the second leg, participants were signaled to rotate and walk to the origin. For real world wheelchair propulsion, participants were seated in the chair and the experimenter guided the movement of the wheelchair by standing behind it and reaching forward to activate the joystick. The experimenter followed a path outlined on the floor that indicated the precise distance required to travel and angle to turn. For return paths, participants either walked (walking condition) or propelled their wheelchair (wheelchair condition) back to the origin (see **Figures 1A,B**, respectively). After their position was recorded, they were moved away from their end position and briefly removed the blindfold in order to allow them to re-orient to the environment. This reduced the potential desire to remove the blindfold at unscheduled moments during subsequent trials when they may perceive some confusion about their location. Triangles were counterbalanced according to the length of the leg and angle turned. The length of the first and second leg ranged from 1.2 to 5.5 m and the turning angle was either 36 or 104°. The starting position for each triangle was varied.

In the distance reproduction task (DRT), participants were guided through a linear displacement of 3.0, 6.1, and 9.1 m. When they came to a complete stop, participants were then rotated toward the origin and signaled to travel back to the starting position. After their end position was recorded, participants were escorted away from the end position before briefly removing the blindfold as indicated above. The starting position varied for each distance.

In order to ensure the experimenter provided a similar walking and wheelchair propulsion velocity for young and older individuals, a sub analysis of movements was analyzed. The walking speed for the experimenter was 0.78 m/sec and 0.69 m/sec, for young and older participants, respectively, and these differences were not statistically significant ($p = 0.45$). Likewise, the movement speed for the experimenter when pushing the wheelchair was 0.65 m/sec for younger individuals and 0.56 m/sec for older individuals. These differences were not statistically significant ($p = 0.17$). Similar velocities (0.6 m/sec) were used by the experimenter during walking and wheelchair propulsion conditions in the Allen et al. (2004) study.

VIRTUAL ENVIRONMENT-TRIANGLE COMPLETION AND DISTANCE REPRODUCTION TASKS

When performing the TCT and DRT in the VE, participants first passively viewed motion of the linear path for the DRTs and then the outbound paths, separated by a rotation for the TCTs (see **Figure 1C**). Speeds of movement during passive viewing were matched for both the TCT and DRT.

Three DRTs (3.0, 6.1, and 9.1 m) and six TCTs were completed each condition (walk, wheelchair, and VE). One additional practice trial preceded two test trials for each condition × task combination (see **Table 1** for details about the triangles).

PRACTICE SESSION

For real world conditions, participants were familiarized with the testing environment by performing specified movements in the testing area. For the walking condition, individuals were guided through the movement by the experimenter, first without, then while wearing the gait belt, blindfold, and noise blocking earphones. The experimenter explained to the participants that a tap on the shoulder would be used to indicate reference movement onset and movement termination. When the reference movement distance was completed, participants were rotated and then instructed to reproduce the distance traveled or to return to

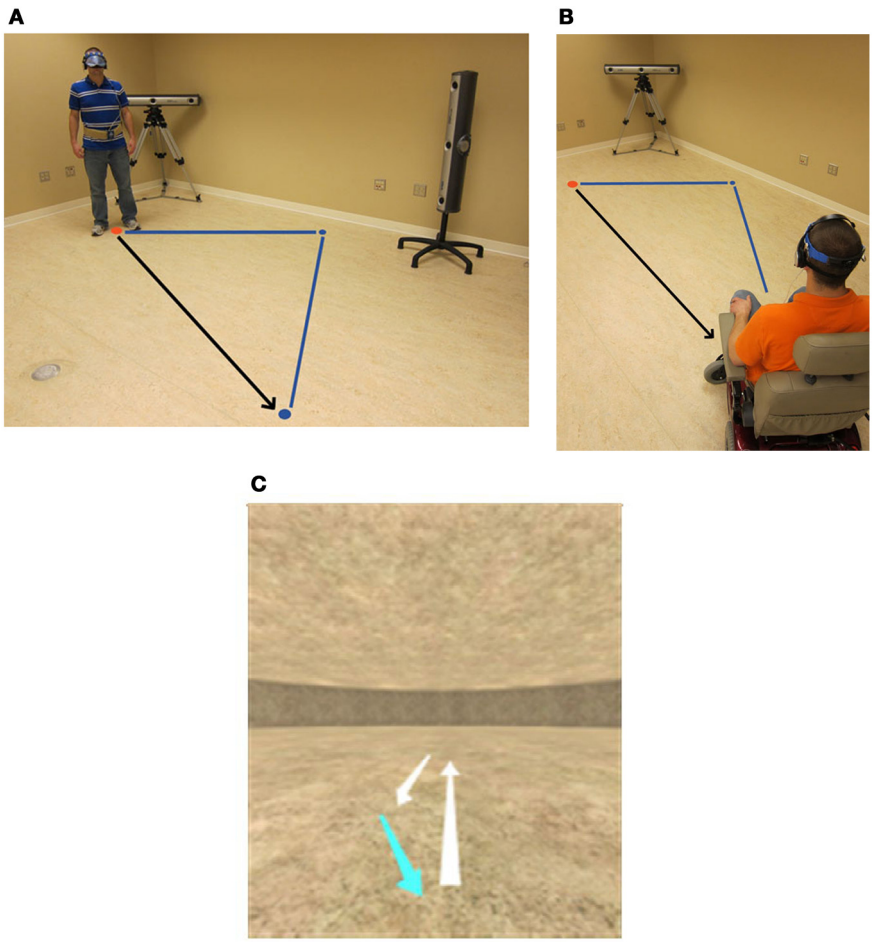

FIGURE 1 | Schematic of experimental setup: participants wore noise reducing headphones and a blindfold during guided walking (A) and wheelchair propulsion (B) conditions. Data were collected from reflective markers placed on a halo structure worn on the head of the participant. VE condition consisted of passively viewing a movement trajectory on a computer monitor **(C)** then moving a joystick when responding to the active portion of the task. Guided movements (lighter shaded lines) and participants movements (darker shaded lines) are shown on the schematic.

Table 1 | Six triangles were presented to the participants.

	T1	T2	T3	T4	T5	T6
Leg 1 (m)	1.2	5.5	2.4	1.8	2.4	5.5
Turning angle (degree)	36	36	36	104	104	104
Leg 2 (m)	1.8	2.4	5.5	1.2	5.5	2.4

The distance of the first and second leg and turning angle were counterbalanced across triangles. Triangles performed in the VE were scaled identically.

the origin of the triangle. Two practice trials were performed to ensure individuals understood the instructions.

For the wheelchair condition, participants were seated in the wheelchair and were requested to travel in a straight line and maneuver around cones placed equidistance apart on the floor by moving the joystick located on the armrest of the wheelchair. Following this, the experimenter propelled the participant through the testing environment. This was done first with and then without the participant wearing the blindfold and noise blocking earphones. Likewise, the experimenter explained that a tap on the shoulder would be used to indicate reference movement onset and movement termination. Additional time (approximating 15 min) was provided to practice this task when compared to that needed to practice walking tasks, in order to allow the individual to become comfortable using the controls.

A practice session was also provided prior to participating in the VE condition. Participants viewed a cubic room that contained landmarks. They first were provided with instruction on the use of the joystick and then used the joystick to move freely around the room. When participants demonstrated competence with the use of the joystick in moving freely around the room, competency with joystick control was verified by completing a speed task. The speed task consisted of traveling through a long and circuitous virtual hallway; participants were required to travel through the hallway in 120 s or less to verify joystick competence.

TESTING SESSION

For real world conditions, the experimenter guided the participants through the testing paths, and then tapped them on the shoulder to signal when it was time to reproduce the distance traveled or return to the origin of the triangle. When individuals moved beyond the detectable range of the positions sensors, distance and angular measurements of end positions were taken with a measuring tape and goniometer. Trials were also terminated if safety was a risk (for example, if bumping into a wall was imminent). For the VE condition, participants first passively viewed motion of a linear distance in a long hallway, and then were asked to use a joystick to travel the same distance they previously viewed. Speeds of movement during passive and active viewing were deliberately mismatched to prevent participants from using a simple time-counting strategy to perform reproductions. Participants were informed of this mismatch and told explicitly not to use time estimation to reproduce the distances and that attempting to do so would be futile.

DATA COLLECTION

For real world conditions, movement data were recorded from the Optotrak Certus™ motion capture system. Movement data detected from at least three active markers on the halo were used to calculate a centroid using Matlab software that, in turn, provided a single trajectory corresponding to each person's movements. When movements were beyond the detectable range of the position sensors, floor measurements were taken. Movement data for the VE condition were collected within Unreal Tournament 2003. Data collected for all conditions were processed using customized Labview software.

DATA ANALYSIS

In order to evaluate the error across different distances, the relative error was calculated for each condition (walk, wheelchair, and VE) and task (DRT, TCT) combination.

The relative distance error for DRT and TCT was calculated as a proportion of the distance traveled relative to the required distance, (Relative distance error = $|dactual - d\text{required}|/d\text{required}$). The relative rotation error for TCT was calculated as a proportion of the angle turned relative to the required rotation, (Relative rotation error = $|ractual - r\text{required}|/r\text{required}$). Age differences for assessments and control measures were reported as means ± SD.

RESULTS

Independent sample *t*-tests showed no statistically significant differences for MMSE scores (29.0 ± 1.2 and 28.5 ± 1.4) years of education (15.6 ± 1.9 and 15.0 ± 2.0), motion sickness symptoms or fatigue between young and old groups ($p > 0.05$), respectively. In addition, there were no statistically significant differences between young and older individuals for visual screening and walking assessments or reports of motion sickness post-participation in the VE condition (p's > 0.05) (see **Table 2**).

Table 2 | Mean (SD) for screening assessments in young and older adults.

	Young	Older	*P*-values
MMSE	29.0 (1.2)	28.5 (1.4)	0.13
Education (years)	15.6 (1.9)	15.0 (2.0)	0.41
Motion Sickness	2.1 (1.7)	1.9 (1.9)	0.48
Fatigue	0.27 (0.45)	0.38 (0.50)	0.51
Fatigue (% reporting 0/1)*	72.7/27.3	62.5/37.5	0.50
Contrast sensitivity	1.7 (0.04)	1.7 (0.06)	0.23
Ishihara color-blindness	20.2 (1.0)	20.4 (0.8)	0.58
TUG (s)	8.4 (1.7)	9.1 (2.3)	0.23
Speed test (s)	93.3 (3.2)	100.4 (5.7)	0.08

*Independent t-tests were conducted with the exception of chi square test *.*

RELATIVE ERROR FOR TRIANGLE COMPLETION TASKS

Analyses of the TC tasks involved decomposing the error as a function of the required linear distance traveled and angle turned to understand how each individual component contributed to overall performance. A repeated measures ANOVA was conducted to test for main and interaction effects for condition (walk, wheelchair, and VE) and triangle (1–6) with age as the between subjects factor and relative distance error and relative rotation error as dependent variables.

There was a significant main effect for age [$F_{(1,\ 36)} = 6.8$, $p < 0.05$] with older adults showing greater errors than young adults and a significant main effect for condition [$F_{(2,\ 72)} = 22.8$, $p < 0.0001$] with greater errors found in the VE condition when compared to the wheelchair; and in the wheelchair condition when compared to the walking condition. There were no significant main effects of triangle [$F_{(5,\ 180)} = 1.1.$ $p > 0.05$], thus triangle was collapsed across conditions for subsequent comparisons and no significant main effects for gender [$F_{(1,\ 36)} = 0.22$, $p > 0.05$]. A significant two-way age x condition interaction [$F_{(2,\ 72)} = 7.6$, $p < 0.01$] indicated that age differences were specific to condition tested.

Pairwise comparisons based on estimated marginal means determined that older individuals, mean (SE); 47.8 (4.1) generated greater relative distance errors ($p < 0.05$) than younger individuals mean (SE); 35.4 (3.6) in the VE condition. For rotation estimations, older individuals generated greater errors in the wheelchair ($p < 0.05$) and VE ($p < 0.01$) conditions mean (SE); 29.1 (3.2), 51.9 (4.1), respectively when compared to younger individuals mean (SE); 18.8 (2.8), 24.1 (3.5), respectively (see **Figures 2A,B**).

In young individuals, relative rotation error was greater in the VE 35.4 (3.6) than walking mean (SE); 27.9 (3.8) condition ($p < 0.05$) and in the wheelchair mean (SE); 30.6 (2.0) than walking condition, showing a tendency toward statistical significance ($p = 0.06$). There were no significant differences between conditions for relative distance error. However, for older individuals, relative distance error was greater in the VE mean (SE); 47.9 (4.1) than walking mean (SE); 31.7 (4.3) condition ($p < 0.01$) and in the VE mean (SE); 47.9 (4.1) than wheelchair mean (SE); 33.3 (2.3) condition ($p < 0.01$). Greater relative rotation error was found in the VE mean (SE); 51.9 (4.1) compared to the wheelchair mean (SE); 29.1 (3.2), condition ($p < 0.01$) and in the VE compared to the walking mean (SE); 17.4 (2.9) condition ($p < 0.01$).

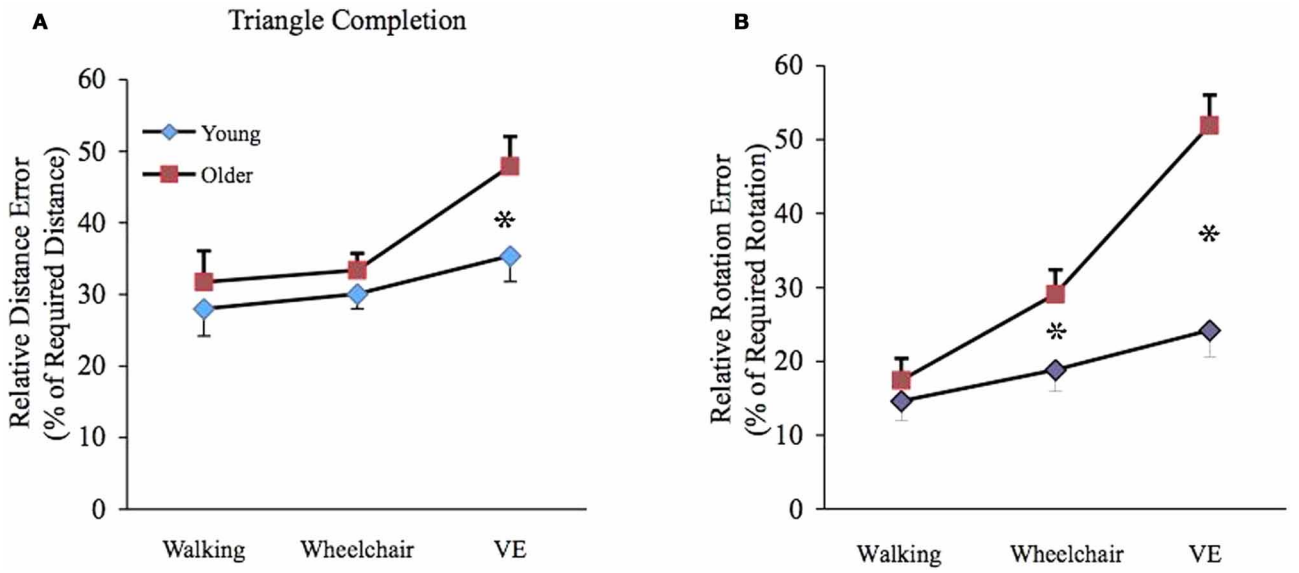

FIGURE 2 | (A) Mean (± SE) relative distance error (RDE) for young (filled diamond) and older (filled square) participants. Age differences were significant in the VE condition (*$p < 0.05$). **(B)** Mean (± SE) relative rotation error (RRE) for young (filled diamond) and older (filled square) participants. Age differences were significant in the wheelchair (*$p < 0.05$) and VE (*$p < 0.01$) conditions.

Likewise, greater error was found in the wheelchair than walking condition ($p < 0.01$).

RELATIVE ERROR FOR DISTANCE REPRODUCTION TASKS

A repeated measures ANOVA with age group as the between subjects factor and condition (walk, chair, and VE) and distance traveled (3.0, 6.1, and 9.1 m) as within-subject factors showed a main effect for condition [$F_{(2, 74)} = 15.0$, $p < 0.01$] and relative distance error as dependent variable. There were no significant main effects for age [$F_{(1, 36)} = 0.28$, $p > 0.05$] or distance traveled [$F_{(2, 72)} = 0.1$, $p > 0.05$]. Pairwise comparisons based on estimated marginal means showed that relative distance error was greater in the VE mean (SE); 22.6 (2.3) than wheelchair mean (SE); 20.8 (1.9) and walking mean (SE); 12.3 (2.0) conditions (p's < 0.05) (see **Figure 3**).

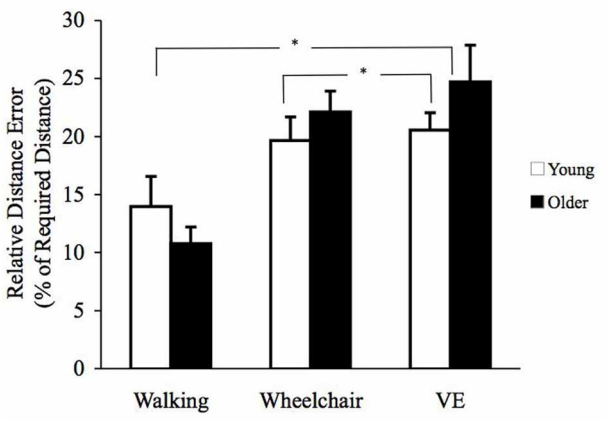

FIGURE 3 | Mean (± SE) relative distance error (RDE) for young (open) and older (filled) participants. Conditions differences were found between VE and wheelchair; VE and walking conditions (*p's < 0.05).

DISCUSSION

Findings from this study showed that age differences in PI abilities were related to the availability of sensory information and task type (DRT, TCT). For DR tasks, older and younger individuals performed in a similar manner showing greater relative error in the VE than wheelchair condition, and in the wheelchair than walking condition. For TC tasks, older individuals were significantly further away from the origin than their younger counterparts for all conditions. When decomposing return to origin errors as a function of rotation and distance estimations, older individuals generated significantly greater rotation estimation errors in the wheelchair and VE conditions, and greater distance and rotation estimation errors in the VE condition when compared to young individuals.

TRIANGLE COMPLETION TASKS

In the present study, there were larger errors when completing the TCT tasks in the VE than in real-world environments. This indicates that participants performed better at PI when they were blindfolded but allowed movement than when they were allowed vision but remained still. In support of this observation, previous work has found that proprioceptive/efferent sources of information have been shown to improve performance of a visually based VE task (Chance et al., 1998; Sun et al., 2004).

Indeed, locomotion was shown to enhance encoding of optic flow information used in VE TCT (Philbeck et al., 2001; Kearns

et al., 2002) suggesting that the availability of vestibular and proprioceptive sensory information contributes to successful updating of movements (Loomis et al., 1993; Philbeck et al., 2008). In addition, Sun et al. (2004) showed that participants who remained stationary while viewing optic flow from a VE head mounted display performed less well in a TCT than subjects who walked or were transported in a wheelchair while viewing optic flow from a VE display. These findings suggest that optic flow by itself does not induce automatic updating of heading direction in a manner similar to that provided by vestibular and proprioception (Loomis et al., 2002). Our results are consistent with this interpretation.

When decomposing the relative contribution of rotation and distance estimations to TCT errors in the VE, greater errors were found for all rotation estimations across all triangles in older than young individuals. Similar errors in rotation were found for older individuals in other studies (Mahmood et al., 2009; Harris and Wolbers, 2012). Mahmood et al. (2009) showed that estimating the absolute rotation of a PI task contributed significantly to the overall error. However, Harris and Wolbers (2012) reported that rotation error was largely due to under rotating.

Further, the age effects found in the VE may be related to age-related differences in the processing of visual motion, especially optic flow (Atchley et al., 1998). Indeed, processing of self-motion cues is related to higher order processing (Wolbers et al., 2007) which may be vulnerable with aging. Kavcic et al. (2011) showed that older individuals required higher thresholds for detecting optic flow than younger individuals. In their study, participants were asked to judge which field on the visual display (left or right) was moving faster than the other. Older individuals required faster movements in opposing directions to distinguish differences in movement speed. However, this is in contrast to findings from others (Atchley et al., 1998; Billino et al., 2008a) who found optic flow detection to be unaffected by age suggesting that processing visual information is context-dependent and may be explained by differences in methodologies used to test for detection thresholds (Billino et al., 2008b). Indeed, Mossio et al. (2008) found estimating distances traveled in VE tasks when using optic flow were highly dependent on the strategy used by the participant and specific features associated with the presentation of visual information, such as texture regularity and depth cues, for example.

Allen et al. (2004) found no age difference in TCT in the walking condition. However, they found significant age differences in the same task following passive conveyance in the wheelchair, which they concluded, was largely the result of errors in estimating rotation. These findings are similar to the present results showing that the type of available sensory information distinguishes age differences in PI.

Tasks performed in the wheelchair condition restrict visual and proprioceptive feedback, forcing participants to rely on vestibular input. This finding is compatible with the observation that older individuals have greater difficulty using vestibular information when visual information is not available (Deshpande and Patla, 2007) and when there is decreased sensitivity of proprioceptors (Deshpande and Patla, 2007). In addition, as pointed out by Agrawal et al. (2009) degeneration of the vestibular system (Johnsson, 1971) may not be compensated for by proprioceptive information in older adults.

Vestibular and proprioceptive information also is critical for PI in animals (Mittelstaedt and Mittelstaedt, 1982; Etienne et al., 1988) Animals with vestibular damage showed declines in navigation when landmark cues were absent (Cohen, 2000; Stackman and Herbert, 2002), a finding which parallels the observation that labyrinthine-defective human subjects have difficulty estimating and reproducing the length of a path or a previously seen target (Glasauer et al., 1994, 1999).

DISTANCE REPRODUCTION TASKS

Previous studies have shown that young individuals can accurately estimate path length following passive translation (Israel and Berthoz, 1989) and guided walking (Glasauer et al., 1994, 2002; Klatzky et al., 1990). However, no previous study has compared age differences in distance estimations across three different perceptual conditions.

In the present study, the DRT showed no age differences in performance, and both younger and older adults showed a similar magnitude of errors as a function of condition (VE>W/C>Walk). Our lack of age-differences in DRT is somewhat at odds with Mahmood et al. (2009) who showed that older individuals were less accurate in reproducing long (but not short) distances than younger individuals. However, there were substantial differences between studies in both the speed of movements and the distances traveled. In the Mahmood et al. (2009) study, distances ranged from 22.9 to 140.2 virtual m, and the speed of movement averaged 11.2 m/sec, which comes closer to replicating traveling by a motorized vehicle. Similarly, movement speeds were faster in the Harris and Wolbers (2012) study compared to the present study, which may explain a lack of age differences. In the present study, the VE speeds averaged 0.9 m/sec and distances traveled average 5.8 m. This suggests that when optic flow information is presented at slower speeds and/or over shorter distances, performance may improve in older adults resulting in negligible age differences for DRTs.

This investigation of age-related differences in PI abilities is limited by its relatively small sample size and cross sectional design, offering comparisons between older and young adults at a single time point. Indeed, longitudinal studies may offer a better representation of PI abilities when increasing age may be accompanied by declines in sensorimotor and cognitive function. In addition, the age range of the older adults (70.1 ± 6.4 years), health status and screening scores (MMSE scores $>$ 28/30) indicate an active, healthy cohort, the results of which may not translate to a more at-risk population. Another potential limitation to the study was the lack of counterbalancing of task order. The VE condition was presented last to all participants leading to a possible confounding with subject fatigue that could potentially differ by age group. However, the fact that younger and older participants did not differ in fatigue at the end of the study suggests that this lack of counterbalancing likely played a minimal role in the age-differences observed.

We also acknowledge that factors other than sensory differences between conditions could contribute to the age differences observed herein. Among these additional factors may be age

difference in working and episodic memory or spatial cognition and spatial imagery, age differences in interfacing with unfamiliar technological devices or possibly other factors that were not measured in the present study.

In sum, specific age and condition effects found in the present study may be explained with reference to the availability of sensory information (visual, proprioceptive, and vestibular). Findings from this study could be used to target interventions at reducing wayfinding difficulties in older adults. In addition, the paradigm used in this study is sensitive to detecting small changes in performance and future research may indicate its potential to serve as an indicator to track the onset and progression of dementia over time.

ACKNOWLEDGMENTS

Del Harder Research Award, Detroit Medical Center, Detroit, Michigan awarded to Diane E. Adamo. Special thanks to Bernard Martin for assistance with design of the data analysis software.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 02 May 2012; accepted: 29 August 2012; published online: 25 September 2012.

*Citation: Adamo DE, Briceño EM, Sindone JA, Alexander NB and Moffat SD (2012) Age differences in virtual environment and real world path integration. Front. Ag. Neurosci. **4**:26. doi: 10.3389/fnagi.2012.00026*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 13 September 2012
doi: 10.3389/fnagi.2012.00025

Remote spatial memory in aging: all is not lost

R. Shayna Rosenbaum[1,2]*, Gordon Winocur[2,3,4,5], Malcolm A. Binns[2,6] and Morris Moscovitch[2,3,7]

[1] Neuroscience Graduate Diploma Program, Department of Psychology, York University, Toronto, ON, Canada
[2] Rotman Research Institute, Baycrest, Toronto, ON, Canada
[3] Department of Psychology, University of Toronto, Toronto, ON, Canada
[4] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[5] Department of Psychology, Trent University, Peterborough, ON, Canada
[6] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[7] Department of Psychology, Baycrest, Toronto, ON, Canada

Edited by:
Thomas Wolbers, University of Edinburgh, UK

Reviewed by:
Eric Blalock, University of Kentucky, USA
Sue Becker, McMaster University, Canada

***Correspondence:**
R. Shayna Rosenbaum, Department of Psychology, Neuroscience Graduate Diploma Program, York University, 4700 Keele St., Toronto, ON M3J 1P3, Canada.
e-mail: shaynar@yorku.ca

The ability to acquire and retain spatial memories in order to navigate in new environments is known to decline with age, but little is known about the effect of aging on representations of environments learned long ago, in the remote past. To investigate the status of remote spatial memory in old age, we tested healthy young and older adults on a variety of mental navigation tests based on a large-scale city environment that was very familiar to participants but rarely visited by the older adults in recent years. We show that whereas performance on a route learning test of new spatial learning was significantly worse in older than younger adults, performance was comparable or better in the older adults on mental navigation tests based on a well-known environment learned long ago. An exception was in the older adults' ability to vividly re-experience the well-known environment, and recognize and represent the visual details contained within it. The results are seen as analogous to the pattern of better semantic than episodic memory that has been found to accompany healthy aging.

Keywords: aging, hippocampus, landmark recognition, mental navigation, recollection, remote memory, route learning, spatial memory

INTRODUCTION

Healthy aging is characterized by a variety of neural changes, with the hippocampus among the most prominent brain structures to be affected (e.g., Jernigan et al., 2001; Raz et al., 2005; Park and Reuter-Lorenz, 2009). These changes are accompanied by difficulties in forming and retaining new spatial memories of allocentric relations among locations (e.g., Barnes, 1979; Winocur and Gagnon, 1998; Head and Isom, 2010; Harris and Wolbers, 2012). Whereas the hippocampus is needed to support such spatial representations (e.g., O'Keefe and Dostrovsky, 1971; Morris et al., 1982; Wolbers and Büchel, 2005; Nedelska et al., 2012; but see Corkin, 2002), it does not appear to be needed for all aspects of remote spatial memory for environments encountered long ago[1] (Rosenbaum et al., 2000, 2004, 2007; Maguire et al., 2006). However, there is little information about the effects of aging on remote spatial memory. The current study examines the integrity of remote spatial memory in healthy young and older adults.

The ability to flexibly represent the external world in order to navigate efficiently between spatial locations in both new and familiar environments is essential for independent living. Despite its importance, there is a long-standing debate about the neural substrate of allocentric spatial memory for large-scale environments, particularly those that were experienced long ago. Central to this debate is the role of the hippocampus. A long-standing theory is that the hippocampus is always necessary for supporting allocentric spatial memory ("cognitive maps") to navigate an environment, no matter how long ago that memory was acquired, as opposed to egocentric representations of the environment within body-centered coordinates (O'Keefe and Nadel, 1978; Bird and Burgess, 2008). A derivative of this theory views scene construction as the central role of the hippocampus. Scene construction involves the retrieval and integration of relevant details into a coherent spatial framework within which details of personal memories can be re-experienced and manipulated into imagined new experiences (Byrne et al., 2007; Hassabis et al., 2007; Hassabis and Maguire, 2009). Based on these theories, one might predict that both recent and remote spatial memory and navigation that rely on allocentric cues would be affected by hippocampal damage. An alternative prediction is that deficits in scene construction may only impair the detailed perceptual representations of an environment, such as is required to recall or imagine scenes, but not for navigation.

Another view that may be considered complementary is that the hippocampus has a time-limited role in representing coarse, schematic, or semantic-like aspects of spatial memory, but is needed always for representing rich, detailed episodic-like aspects (Rosenbaum et al., 2001; Moscovitch et al., 2005; Winocur et al., 2010a). By schematic representations, we mean map-like representations that contain information about landmarks, their location, and relation to one another, which are needed for

[1] The term "remote" is used to describe memories that are temporally distant and is not used in the current paper in reference to spatial distance.

navigation[2]. From our view, this schematic representation is impoverished with respect to perceptual details that are incidental to navigation, such as the appearance of houses (Rosenbaum et al., 2000) and even of the landmarks themselves. We consider these more detailed aspects as part of the representation that allows for a rich re-experiencing of an environment. The distinction between schematic and detailed spatial representations, which may or may not be orthogonal to allocentric vs. egocentric frameworks, is based on findings from lesion and neuroimaging studies. Amnesic people with hippocampal lesions show evidence of relatively preserved navigation but impaired memory for perceptual details of environments learned long ago (Teng and Squire, 1999; Rosenbaum et al., 2000, 2005; Maguire et al., 2006). These findings are consistent with evidence from neuroimaging studies showing a relative lack of hippocampal activation for mental navigation in the same environments (Rosenbaum et al., 2004, 2007; Hirshhorn et al., 2012). The hippocampus is known to suffer structural and functional decline with age. Similar to hippocampal amnesic patients, older adults show a decline in autobiographical episodic memory for both recent and remote events and associated recollection processes, but relative preservation of semantic memory and associated familiarity (e.g., Davidson and Glisky, 2002; Levine et al., 2002; Piolino et al., 2006).

The changes in declarative/relational memory that do occur appear to relate to significant atrophic changes in hippocampal volume associated with aging (Yonelinas et al., 2007). Aging has also been associated with spatial disorientation in recently encountered environments in both animals and humans in relation to hippocampal volume loss (e.g., Driscoll et al., 2006; Moffat, 2009). A study of older adults suggests that this impairment extends to the re-experiencing of familiar routes from an environment that was traveled extensively in the past, which is correlated with neuropsychological tests of hippocampal function and autobiographical episodic memory (Hirshhorn et al., 2011). Nevertheless, the ability to represent the spatial distance between landmarks located in the same environment does not appear to be affected, though comparison of the older adults' remote spatial memory performance was not made with a younger group. In a more direct investigation, aged rats with prior exposure to a complex "village" environment showed significantly better memory for allocentric spatial relations among locations contained within that environment than age-matched rats who were naïve to the environment (Winocur et al., 2010a). The experienced aged rats performed slightly worse than they had as young rats during initial training, but better than a separate group of young rats not previously exposed to the environment, indicating both preserved remote spatial memory and impaired new spatial learning in old age.

Overall, the findings suggest that spatial representations of well-learned environments formed long ago are relatively impervious to the effects of aging and, together with earlier findings of similar preservation in young rats with hippocampal lesions (Winocur et al., 2005, 2010a), do not depend on the hippocampus. To our knowledge, however, systematic examination of remote spatial memory in young vs. older adults has not been attempted in humans. If the hippocampus, which functionally declines with age, is not needed for various aspects of remote spatial memory, particularly those which support navigation, then aging should not affect performance on spatial memory tasks based on an environment that was extensively navigated in the past, even if it affects spatial learning in newly encountered environments. Retention and retrieval of perceptual details of an environment, whether experienced recently or long ago, however, should be impaired in older adults as these always are dependent on the hippocampus. The data presented in the current study support these predictions.

[2]At the moment, we do not know how integrated the information on the map is and what kind of fine-grained information this kind of map can support. It is possible that this representation contains a series of local map-like representations or route knowledge that is strung together.

MATERIALS AND METHODS

PARTICIPANTS

A group of 14 healthy older adults aged 65–85 years (half male; 13 right-handed) were recruited from the Baycrest participant pool for monetary compensation. Comparisons were made with a group of 14 young adults aged 18–30 years (half male; 13 right-handed) recruited from the Baycrest participant pool for monetary compensation and the York University Undergraduate Research Participant Pool for course credit. Demographic information and other descriptive data are summarized in **Table 1**. Participants were matched for years of education, fluent in English, free from a history of neurological and psychiatric illness, and lived in Toronto for a minimum of 10 years. None of the older participants met criteria for dementia based on the MMSE or MoCA. The study received approval from the York University and Baycrest research ethics boards.

MATERIALS AND PROCEDURE

Participants' remote spatial memory was tested for mental navigation amid landmarks and for the visual identity of those

Table 1 | Demographic characteristics of the younger and older participants.

		Younger		Older	
		Mean	**SD**	**Mean**	**SD**
Age (years)		22.21	4.00	72.21	6.31
Education (years)		14.36	1.15	15.29	1.98
Living in Toronto (years)		18.21	4.66	50.5	16.16
Visit frequency[a]		3.82	1.38	2.71	1.12
Navigation ability[b]	New environments	3.54	1.15	4.04	0.89
	Familiar environments	4.43	0.85	4.5	0.65

Note: SD, standard deviation.

[a]Based on scale ranging from 1 to 5, where 1 = no more than once a year, 2 = 1 to 2 times per year, 3 = once a month, 4 = once a week, and 5 = more than once a week.

[b]Based on subjective ratings on a Likert scale, ranging from 1 (difficulty navigating/always disoriented) to 5 (navigates with ease/never disoriented).

landmarks located in a city environment (downtown Toronto, approximately 5 square km). The environment was experienced approximately 2–3 times per week for at least 10 years by all participants and up to 45 years ago by the older participants. Most of the older participants rarely experienced the environment in the last 5 years. The tasks were designed to simulate the demands of negotiating through large-scale space, with mental navigation tasks varying in terms of their demands on allocentric (tasks 1–4) vs. egocentric processing (tasks 5 and 6; see Ciaramelli et al., 2010, for a detailed rationale for task classification). Comparisons in remote spatial memory performance were made with spatial memory acquisition on a route learning test. Tasks were presented in a fixed order, as follows.

Mental navigation tests (Toronto Public Places Test; TPPT)

Proximity judgments. In a test of relative distance judgments, participants indicated which of two Toronto landmarks was closest to a third reference landmark. The actual distance among the 10 sets of landmarks for each environment varied from trial to trial, and half of the trials were more demanding (i.e., the difference in distance between the reference landmark and either of the choice landmarks was less than 1 km).

Distance judgments. Participants were asked to provide numerical judgments of absolute distance between each of 10 pairs of landmarks located in downtown Toronto in their preferred unit of measure (i.e., km or miles). A sample trial was administered prior to testing in order to give the participants an indication of scale. The actual distances between landmarks were varied and randomly intermixed across trials. The mean deviation of the judged distances from the actual distances in km was calculated for each trial and averaged to derive absolute error scores.

Vector mapping. In a test of allocentric distance and head-direction between landmarks, participants were asked to draw arrows indicating the correct distance and direction from a location specified by a mark to an unmarked landmark on 10 maps of downtown Toronto that included lines indicating northern and southern downtown city limits. Deviation of estimates from actual directions in degrees and distances in km was calculated for each trial and averaged to derive absolute error scores.

Landmark sequencing. Ten randomly ordered names of landmarks located along a north-south route were presented, and participants were to order the landmarks in the sequence that would be passed during a mental walk of the route.

Blocked routes. Participants were asked to simulate taking shortcuts in a task requiring a change of route from the most direct route between a pair of landmarks. There was a total of 5 such trials, each consisting of 2 to 4 choice points at which to turn right or left, for a maximum score ranging from 11 to 16 per participant. Partial points were given for impoverished descriptions of routes that otherwise led to the specified destination. At the end of the task, participants were additionally asked whether they felt that they were remembering the simulated navigation episodes from a first-person perspective (i.e., as being actually involved in the episode; e.g., driving or walking on the streets) or from a third-person perspective (i.e., as being an observer of the episode, or adopting a survey perspective), and whether they had experienced the routes as vivid and rich in detail while mentally navigating them.

Landmark appearance

Participants were asked to distinguish between photographs of downtown Toronto landmarks and of buildings that are structurally similar to those located in downtown Toronto but that have never been encountered by the participants. The stimulus set included a total of 25 landmarks and 25 distractors. All photographs were taken from an unobstructed view and were digitally scanned and adjusted for luminance and contrast. For each photograph, participants were to decide if the landmark is familiar, and if so, to identify it by name and location or by some other means if necessary (e.g., type of building, decade in which it was established, function).

Baycrest route learning test

A route learning test previously found to be sensitive to hippocampal function in Alzheimer's disease (Rosenbaum et al., 2005) was adapted for the present study to assess spatial acquisition. Participants were taken on a novel route through two floors of Baycrest, where the Rotman Research Institute is located. Four of the older participants had visited Baycrest prior to the current study, and none had traversed the particular test route. There were 16 choice points along the route where participants had to decide whether to turn right or left or to continue straight. The route covered three floors of the hospital, and participants relied on an elevator to travel between floors. Four legs of the route included large windows with views to distal outdoor cues; the remainder of the route did not include views to the outside.

Procedure. The learning phase involved a 15-min experimenter-led tour of the route. Participants were instructed to pay attention to the route and its visual features as reminders of where to turn because they would later be asked to lead the experimenter on the same route. While on the tour, the experimenter did not point out landmarks or turns, other than the destination floor when the elevator was taken. During the test phase, the participant led the experimenter through the route, with errors recorded and corrected to maintain the flow of the route. After a 30 min filled break, during which the landmark appearance test was administered, participants were asked to lead the experimenter through the route a final time.

STATISTICAL ANALYSES

Most of the tasks (Proximity Judgments, Landmark Sequencing, Blocked Routes, Landmark Identification, and Baycrest Route Learning) generated error count data as the outcome variable of interest. For these measures we entered number of errors as the dependent variable in a Poisson regression to examine differences between the younger and older participants. We adjusted the null hypothesis tests using the deviance scaling option to compensate for under- or over-dispersion. An offset variable was included for

the Blocked Routes test to accommodate differences in the total number of streets used for each trial per participant. The remaining tasks (Distance Judgments, Vector Mapping, and Landmark Recognition) generated outcome variables with reasonably bell-shaped distributions, and these were entered into an analysis of variance (ANOVA) with Group (young vs. old) as a between-subject factor. In order to examine the effects of differences in exposure to downtown Toronto on the main effect of age, the number of years living in Toronto and frequency of recent visits to the downtown core (i.e., within the past 5 years) were included individually as covariates in all models. Finally, correlations in performance on the experimental measures, stratified by age, were calculated. All hypothesis tests are performed at an alpha level of 5%.

RESULTS

As indicated by the descriptive data in **Table 1**, the young adults visited downtown Toronto more frequently within the past 5 years compared to the older adults, whereas the older adults lived in Toronto for a significantly longer time than the young adults. Although each of the variables were included separately as covariates in the analyses, the lack of overlap in groups on the latter variable may present a challenge to interpreting conditional age effects in test performance. Surprisingly, subjective ratings of navigation ability were lower for the young adults compared to the older adults for new environments and indistinguishable for familiar environments. Participants' performance on all spatial memory tests is presented in **Table 2**.

MENTAL NAVIGATION TESTS (TPPT)

Proximity judgments

Poisson regression on error count (collapsed across easy and difficult trials) revealed no significant effect of group, $p = 0.88$, even when taking into account frequency of visits, $p = 0.86$. It remains possible that older participants perform worse when number of years living in Toronto was taken into account, though this sample produced equivocal results, $X^2(1, N = 28) = 1.98$, $p = 0.16$.

Distance judgments

ANOVA on mean deviation of estimates from actual distance (in km) revealed no significant effect of group, $p = 0.2$. Likewise, analysis of covariance (ANCOVA) revealed no significant effect of frequency of visits or number of years living in Toronto, $p > 0.26$ in both cases, even when an outlier was withheld from the analyses.

Vector mapping

ANOVA on deviation of estimates from actual distance (in km) revealed no significant effect of group, $p = 0.15$. ANCOVA revealed no significant effect of group when number of years living in Toronto was taken into account, $p = 0.32$, even when an outlier was withheld from the analyses. There was a marginally significant effect when frequency of visits was taken into account, $F_{(1, 26)} = 3.92$, $p = 0.06$, suggesting that the older adults performed better than the younger adults in estimating vector distance.

ANOVA on mean deviation of estimates from actual direction (in degrees) revealed a significant effect of group, $F_{(1, 26)} = 4.59$, $p = 0.04$, such that older adults performed better than younger adults. ANCOVA revealed the effect of group to be larger when frequency of visits was taken into account, $F_{(1, 26)} = 8.66$, $p = 0.007$[3]. This result is presented in **Figure 1A**.

[3]Withholding data from an influential participant reduced the effect of group to marginal. This was true both without and with the frequency of visits covariate, $p > 0.06$ in both cases, with the effect continuing to be in the predicted direction.

Table 2 | Performance of young and older participants on experimental tasks.

Experimental task		Young		Old		*p*-value	*d*	pd	e^{β}
		Mean	SD	Mean	SD				
MENTAL NAVIGATION									
Proximity	error	1.21	1.42	1.14	0.95	0.88	0.06	−0.06	1.06
Distance	deviation (km)	1.99	2.66	1.04	0.7	0.2	0.49	–	–
Vector	deviation (km)	0.36	0.19	0.28	0.11	0.06†	0.51‡	–	–
	deviation (°)	17.47	7.29	12.38	5.12	0.007†	0.81	–	–
Sequencing	error	1.43	1.45	0.93	1	0.33	0.4	−0.35	1.54
Blocked Route	error	3.64	2.6	2.61	1.06	0.0005†	0.52‡	−0.28	1.99
LANDMARK APPEARANCE									
Recognition	hits – fa	17.64	2.62	13.21	4.56	0.004	1.19	–	–
	hits + fa	26.93	4.5	24.07	5.94	0.04*	0.54	–	–
Identification	error	16.25	3.79	13.69	2.68	0.07	0.78	−0.16	0.77
ROUTE LEARNING									
Immediate	error	1.29	1.14	5.21	2.08	<0.0001	−2.34	3.04	0.25
Delayed	error	0.07	0.27	0.64	0.74	0.01	−1.02	8.14	0.11

Note: fa, false alarm; SD, standard deviation; pd, proportional difference, $\frac{\text{mean}^{\text{old}} - \text{mean}^{\text{young}}}{\text{mean}^{\text{young}}}$; e^{β}, *multiplicative effect of age on error rate.*

**Influential observation withheld; †effect of group, conditional on a covariate (see text); ‡better performance in older adults.*

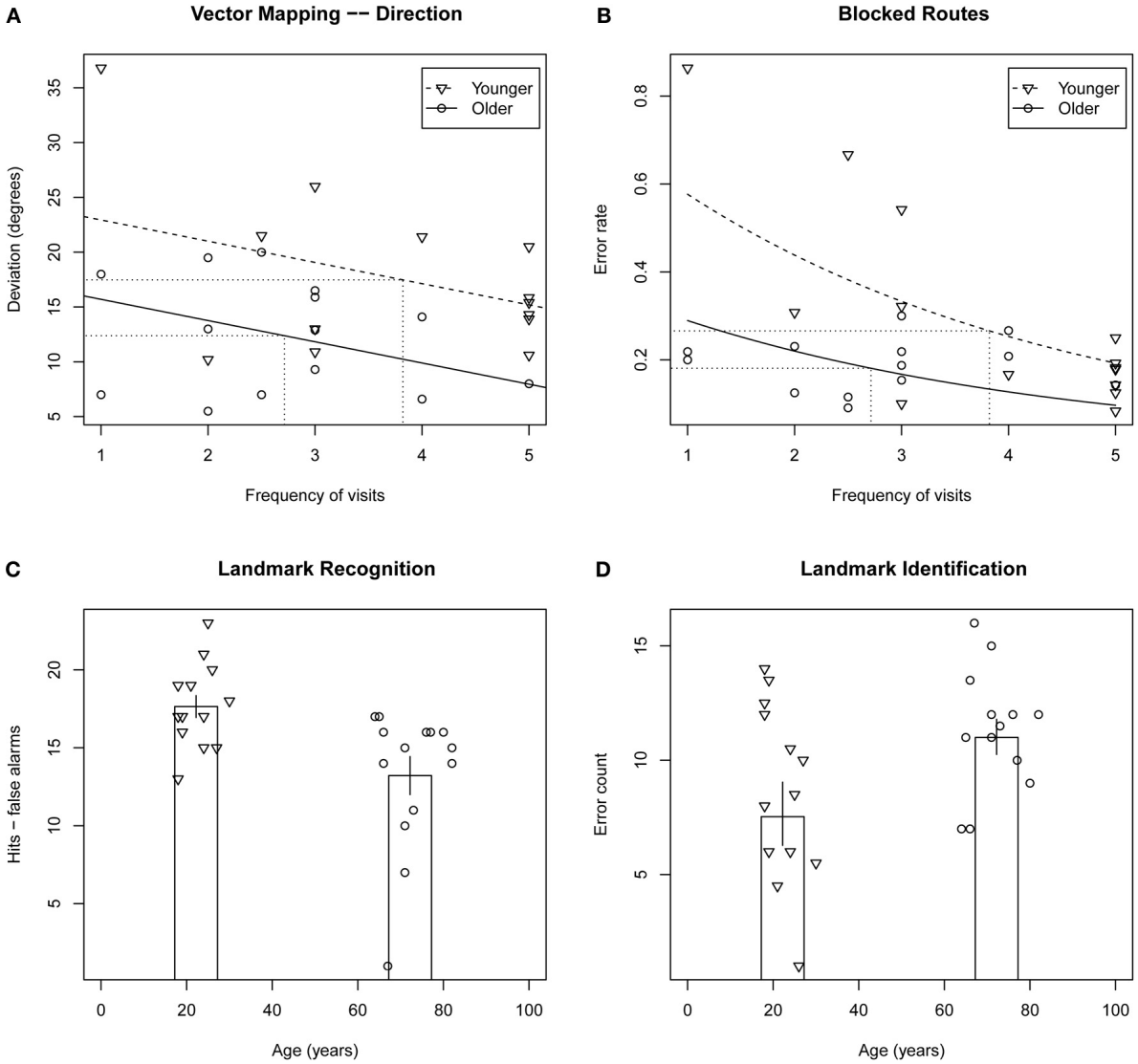

FIGURE 1 | Top row: scatterplots of mental navigation performance versus frequency of visits to Toronto for vector mapping—direction deviation (A) and blocked routes error rate (B), tasks on which older adults performed significantly better than younger adults. Fitted models for younger and older adults are indicated by dashed and solid lines, respectively, and averages for the two groups are indicated by dotted lines. Bottom row: scatterplots of performance on landmark recognition **(C)** and landmark identification **(D)** versus age. Column height indicates average performance for each of the two groups. Error bars indicate ± one standard error.

Landmark sequencing

Poisson regression on error count revealed no significant effect of group, $p = 0.33$, even when frequency of visits and number of years living in Toronto were taken into account.

Blocked routes

Poisson regression on error count when adjusting for the difference in total number of streets between participants revealed that the effect of group was marginal, $X^2(1, N = 28) = 3.18, p = 0.07$, with older participants performing better than younger participants. This observed effect was enhanced when frequency of visits was taken into account, $X^2(1, N = 28) = 12.3$, $p < 0.0005$ (see **Figure 1B**).

SUBJECTIVE RE-EXPERIENCING

With respect to the participants' subjective report, significantly fewer older (7/14) than younger adults (14/14) reported adopting a first-person perspective during navigation in the blocked route task, Fisher's Exact Test, $p = 0.006$. More striking was the finding that 12/14 older adults but only 2/14 younger adults reported that their re-experiencing of the routes in memory lacked vividness and perceptual detail, Fisher's Exact Test, $p = 0.0004$.

LANDMARK APPEARANCE

Landmark recognition

ANOVA on error count for hits minus false alarms revealed a significant effect of group, $F_{(1, 26)} = 9.93$, $p < 0.004$, with the

older participants less able to discriminate between target and distractor landmarks than the younger participants (presented in **Figure 1C**). ANCOVA revealed the effect of group to remain even when frequency of visits and number of years living in Toronto were taken into account, $p > 0.58$ in both cases[4]. ANOVA performed for the sum of hits and false alarms was equivocal with respect to an effect of age group, $F_{(1, 26)} = 2.06$, $p = 0.16$, that was found to be significant when a participant with an unusually high number of false alarms was withheld, $F_{(1, 26)} = 4.61$, $p < 0.04$. The effect indicated a conservative response bias in the older adults and a non-conservative response bias in the younger adults.

Landmark identification

Poisson regression on error count revealed a marginally significant effect of group, $F_{(1, 25)} = 3.32$, $p = 0.07$, with the older participants identifying fewer Toronto landmarks than the younger participants[5] (**Figure 1D**). There was no effect of frequency of visits or number of years living in Toronto.

BAYCREST ROUTE LEARNING TEST

Poisson regression on error count for immediate learning of the new route (sum of runs 1 and 2) revealed an effect of group, X^2 $(1, N = 28) = 25.46$, $p < 0.0001$, such that the older adults performed significantly worse than the young adults. The same was true for delayed learning of the route, X^2 $(1, N = 28) = 6.02$, $p < 0.01$, with the older adults performing significantly worse than the young adults.

CORRELATIONS

Correlational analyses indicated a positive correlation in new route learning between the two trials of the immediate condition, $r_{(26)} = 0.56$, $p = 0.003$, and a negative correlation between the rates of learning from the first to second trial of the immediate condition and from the immediate condition to the delay condition, $r_{(26)} = -0.54$, $p = 0.004$. New route learning in the delay condition was negatively correlated with landmark recognition for hits minus false alarms, $r_{(26)} = -0.48$, $p = 0.01$, and positively correlated for hits plus false alarms, $r_{(26)} = 0.4$, $p = 0.04$. Participants' subjective reports of navigation ability in new environments was positively correlated with their subjective reports of navigation ability in old environments, $r_{(26)} = 0.55$, $p = 0.004$, and negatively correlated with landmark recognition for hits minus false alarms, $r_{(26)} = -0.42$, $p = 0.03$. Correlations among the mental navigation tests of remote spatial memory were mostly positive, ranging from $r_{(26)} = 0.43$ to 0.57, $p = 0.03$ to 0.003. Finally, landmark recognition was positively correlated with landmark identification, $r_{(26)} = 0.55$, $p = 0.004$, whereas landmark identification was negatively correlated with vector mapping–distance, $r_{(26)} = -0.55$, $p = 0.004$, and landmark sequencing, $r_{(26)} = -0.42$, $p = 0.03$.

[4]The age effect remained, even when withholding a potentially influential participant.

[5]Data were not available for one of the older adults.

DISCUSSION

The current study investigated whether the changes in memory that accompany aging affect spatial representations formed long ago (i.e., 10 years ago or more). Older adults performed at least as well as younger adults on a wide range of mental navigation tests of remote spatial memory, even when amount of exposure to downtown Toronto was taken into account. No effect of age was found on proximity judgments, distance judgments, and landmark sequencing, and older adults outperformed younger adults on vector mapping and blocked routes. However, only half of the older adults, as compared to most of the younger adults, reported imagining the routes from a first-person perspective, and nearly all of the older adults, and hardly any of the young adults, reported that their imagined routes lacked perceptual richness and a feeling of re-experiencing. This age difference in self report was accompanied by significantly worse performance in the older adults in visually recognizing and identifying the landmarks for which intact spatial judgments had been made. Preserved performance in older adults was also in stark contrast to significantly worse navigation along a new route, both immediately after learning and following a 30-min delay. These results lend support to the view that the hippocampus is necessary for the establishment of spatial memories and for retaining and retrieving visual and experiential details even of representations formed long ago. However, it does not appear to be needed for representing the schematic attributes that are likely to have been extracted over many years navigating a large-scale environment.

Healthy aging is most often associated with a decline in memory and other cognitive processes, but some types of memory remain unchanged or even improve with age (e.g., Grady and Craik, 2000; Park and Reuter-Lorenz, 2009). In remote memory, episodic memory appears to be most vulnerable to the effects of aging, whereas semantic memory appears to resist such effects. Our work with humans and rats suggests similar distinctions in remote spatial memory. Here we showed that extensive navigation in a city environment over a long period of time leads to long-standing representations of spatial locations that resist disruption from aging. Comparable or better performance was found in old vs. young adults on a range of remote spatial memory tasks previously identified as more likely to be solved in an allocentric reference frame (proximity judgments, distance judgments, vector mapping) as well as those more likely to be solved in an egocentric reference frame (landmark sequencing, blocked routes; see Rosenbaum et al., 2004; Ciaramelli et al., 2010).

The current study does not provide direct evidence of a neuroanatomical substrate for remote spatial memory, but the results in the older adults closely resemble findings in patients with hippocampal damage or degeneration (Teng and Squire, 1999; Rosenbaum et al., 2000, 2005; Maguire et al., 2006). Patients with large bilateral medial temporal lobe (MTL) lesions that affect the hippocampus are able to negotiate their way in most places within premorbidly familiar environments and make a variety of judgments about the spatial relations contained within them. These findings suggest that, with sufficient time and experience, spatial memories can exist independently of the hippocampus

and MTL. In the current study, correlations among the mental navigation tests did not appear to distinguish between tasks pre-classified as allocentric or egocentric, pointing to a blend of reference frames or a separate common strategy to sustain spatial memory performance in the face of other areas of cognitive decline associated with aging. These strategies, and resulting gist-like or schematic representations, may be supported by extra-hippocampal regions specialized for the initial coding of different information about environments within allocentric or egocentric frameworks, or in the integration or translation of the two frameworks. These regions include parahippocampal cortex within the MTL and regions of retrosplenial cortex and posterior parietal cortex to which the MTL regions are strongly interconnected (for a review, see Epstein, 2008). This possibility has been supported by evidence of co-activation of these regions during tests of spatial memory and navigation in neuroimaging experiments (Rosenbaum et al., 2004, 2007; Spiers and Maguire, 2006) and in studies with rats (Maviel et al., 2004; Frankland and Bontempi, 2005; Teixeira et al., 2006).

An alternative account of our findings is that both schematic and detailed, episodic-like aspects of remote spatial memories (discussed below) continue to depend on the hippocampus and that a gist is what survives following partial hippocampal damage. As mentioned, however, studies of patients with extensive damage to the hippocampus bilaterally indicate that even they can navigate in premorbidly learned environments and perform normally on tests of remote spatial memory similar to the ones included in the current study (Teng and Squire, 1999; Rosenbaum et al., 2000). Indeed, a functional neuroimaging study indicated that the little hippocampal tissue that remains in one such case (K.C.) was not differentially activated as he performed remote spatial memory tasks (Rosenbaum et al., 2007). Another possibility is that gist-like spatial memories rely on the hippocampus in older adults, as this structure is not severely damaged as is the case in the amnesic patients that have been studied. But, here again, neuroimaging studies indicate that even young adults do not differentially activate the hippocampus on these tasks (Rosenbaum et al., 2004).

Our results resemble findings in rats which showed that extensive experience in a complex maze as young rats enabled them to retain memory for efficient navigation to specific locations when they got old (Winocur et al., 2010a). Probe trials indicated that the rats' successful performance was, indeed, based on the application of allocentric spatial strategies and not on the use of non-spatial local cues or procedural learning. There are limits to how far we can extend this interpretation to older adults because there were some key differences. Unlike the older adults in the present study who performed normally on these spatial tasks, the aged rats performed slightly worse compared to when they were young. A possible account is that the older adults continued to visit downtown Toronto in recent years, whereas the aged rats were completely restricted from entering the environment for 15 months, about half a rat's lifespan. By contrast, older adults in the present study visited Toronto infrequently and significantly less often than did the young adults in the 5 years preceding the study. In fact, taking frequency of visits into account revealed better performance in the older than in the younger adults, suggesting that the older adults may have used a variety of non-hippocampal strategies to supplement their performance.

Findings of intact performance do not appear to be explained by the number of years that participants lived in Toronto, which was significantly greater for older than younger participants. There may be a minimum amount of experience and/or time (visiting once a week for no more than 10 years) needed for the formation and maintenance of a robust and presumably flexible representation of a real-world environment, but it appears that not much is gained beyond that minimum. Nevertheless, there are other potential confounds that we were unable to control or verify that relate to the nature of exposure to downtown Toronto. For example, the purpose of navigating in downtown Toronto (e.g., location of one's work, home, leisure activities), means of travel (walking, driving, taking public transit), and size or part of downtown Toronto in which one frequents may covary with age. These and other variables may influence the initial encoding and re-encoding of the environment as well as the quality of the representation itself.

Although age differences in representing spatial relations among landmarks and the routes between them were not apparent or favoured older adults, differences did emerge in subjective reports of the experiential quality of mentally navigating the routes. Whereas all of the young adults reported imagining the routes from a first-person perspective, half of the older adults reported a third-person perspective. Even more striking was the finding that the majority of the older participants reported that their re-experiencing of mentally navigating the route lacked vividness and richness of perceptual detail. Hirshhorn et al. (2011) reported a similar paucity of re-experiencing well-known Toronto routes in older adults who otherwise appeared to make accurate proximity judgments based on the same Toronto environment. Importantly, only re-experiencing of routes was correlated with autobiographical episodic memory and other neuropsychological tests of hippocampal function. Although we did not directly investigate the experiential and perceptual qualities of spatial judgments on vector mapping, a task that was also performed better by the older participants, it is possible that perceptual richness and re-experiencing interfered with efficient mental navigation in the younger participants.

The finding that aspects of mental navigation amid spatial locations were intact in the older adults contrasts with impaired recognition of landmarks that occupy those locations, reflecting both a difficulty discriminating between Toronto landmarks and similar-looking foil landmarks, and an overall conservative response rate. The data also suggested worse performance in older than younger adults in providing identifying information (name or other distinctive details) for landmarks that were accurately recognized as being located in Toronto. This additional finding suggests some modality-specific loss of distinctive visual information that enables naming. Object recognition impairment has also been reported in aged rats (Burke et al., 2010; see also McTighe et al., 2010), although these results may also reflect an age-related aversiveness to novelty. The recognition deficit appears to be independent of impaired spatial learning in the rats and resembles impaired pattern separation between stimuli that share visual

features in rats and humans with perirhinal cortex lesions (Burke et al., 2011; for a review, see Graham et al., 2010). Similarly, the landmark recognition deficit described here resembles findings of impaired perceptual discrimination of complex scenes in relation to hippocampal and parahippocampal cortex lesions (Graham et al.). Indeed, we found a similar impairment of Toronto landmark recognition in a former taxi driver who had developed Alzheimer's disease (patient S.B.) in the context of reduced hippocampal and ventral visual cortex volumes (Rosenbaum et al., 2005). This contrasts with intact landmark recognition reported in the former taxi driver T.T. who was post-encephalitic and had bilateral hippocampal damage but intact perirhinal and parahippocampal cortices (Maguire et al., 2006). Park et al. (2004) and Schiavetto et al. (2002) have demonstrated that even when behavioural discrimination of faces, places, and other objects is not required, such object categories are not differentiated in ventral visual cortex to the same extent in old compared to young adults. It remains for future research to determine if the decline in landmark recognition is a consequence of such a lack of neural specificity.

It is possible that detailed knowledge of well-known city landmarks is not essential for navigation, especially when aerial views are presented to capture the landmarks in their entirety, and may, instead be treated as episodic-like details. It is unknown if visual recognition of landmarks is related to re-experiencing those landmarks and other visual features along an imagined route. In a recent study of remote spatial memory in patients with parietal lesions, we found a similar effect of age on the likelihood of reporting detailed, personal episodes associated with Toronto landmarks during a recognition task (Ciaramelli et al., 2010). Impaired autobiographical episodic memory for details of personal events was also found to co-occur with impaired landmark recognition in S.B. (Rosenbaum et al., 2005) and impaired recognition of neighbourhood houses in K.C. (Rosenbaum et al., 2000). In both patients, the impairment was in the context of intact remote memory for spatial locations but impaired learning of new routes. Findings that the perception of spatial elements and vivid recollections of those elements in remote memory are compromised in healthy and pathological aging and in amnesia suggest that the hippocampus is needed for linking different types of spatial details with each other and these to a rich episode.

Finally, we successfully replicated a consistent finding in the literature of impaired spatial learning in aging, which has been demonstrated in rats (Barnes, 1979; Gallagher and Pelleymounter, 1988; Winocur and Gagnon, 1998; Winocur et al., 2010a) and in humans, primarily based on virtual environments (Antonova et al., 2009; Head and Isom, 2010; Etchamendy et al., 2012; Rodgers et al., 2012; see Evans et al., 1984 and Cushman et al., 2008 for findings in real-world environments). The older adults in the current study committed significantly more errors than the young adults in the form of incorrect turns on two trials of an immediate learning condition as well as after a 30-min delay, though both groups showed improvement across trials. Interestingly, older participants seemed not to be cognizant of their deficient learning as they gave similar ratings of good navigational ability in both new and old environments. Both new route learning in the delay condition and ratings of navigational ability in new environments were negatively correlated with the ability to recognize well-known Toronto landmarks. Difficulties perceiving or encoding the appearance of newly encountered landmarks may have hindered route learning in the older adults, though work with rats described above would predict otherwise (see Burke et al., 2011).

Amnesia resulting from hippocampal damage is characterized by a profound inability to form and retain new spatial memories (e.g., Smith and Milner, 1981; Maguire et al., 1996, 2006; Holdstock et al., 2000; Rosenbaum et al., 2000; but see Corkin, 2002). This is supported by data from cellular recordings in animals (O'Keefe and Dostrovsky, 1971; Best et al., 2001; Moser et al., 2008) and humans (Ekstrom et al., 2003), animal lesion studies (Morris et al., 1982; Hampton et al., 2004; Lavenex et al., 2006), and human neuroimaging studies (Spiers and Maguire, 2006; Igloi et al., 2010). Findings like these contributed to the development of Cognitive Map Theory, which specifies that allocentric spatial memory for configural relations among objects located in the environment is uniquely dependent on the hippocampus (O'Keefe and Nadel, 1978; Bird and Burgess, 2008). This theory, and the related scene construction view of hippocampal function, accommodate findings in healthy aging, Alzheimer's disease, and hippocampal amnesia of impaired autobiographical episodic memory (Bright et al., 2006; Gilboa et al., 2006; Kirwan et al., 2008; Rosenbaum et al., 2008) and the construction of scenes and future events (Hassabis et al., 2007; Addis et al., 2011), which inherently involve a spatial framework (Byrne et al., 2007). The hippocampus is believed to sustain and guide this organizing principle, either by virtue of its purported role in processing spatial information or by some general binding process (Rosenbaum et al., 2009; Race et al., 2011). However, these theories do not take into consideration that detailed spatial memories change with time and experience and therefore cannot account for the preserved spatial memories that support navigation in older adults and other people whose hippocampal function is compromised.

Only the Transformation Hypothesis of spatial memory (Winocur et al., 2010b; Winocur and Moscovitch, 2011; see also Rosenbaum et al., 2001 and Moscovitch et al., 2005) can account for both the preserved and impaired spatial memories that we reported. The Transformation Hypothesis is based on the distinction between detailed or episodic-like spatial representations, which are impaired in aging and in hippocampal amnesia no matter how long ago the memories were acquired, and schematic/generic spatial representations of environments, which are resistant to the effects of aging and amnesia after they have been assimilated and stored over time. Spatial memories, like other types of declarative or relational memories, may change over time into a schematic or gist-like form. This process may resemble the "semanticization" of episodic memories in humans, whereby memory traces of repeated events become integrated with pre-existing knowledge in neocortex, stripped of contextual details that would allow for rich re-experiencing of the event. The hippocampus may be needed for the maintenance and retrieval of spatial details that are embedded within an episodic representation but not for a spatial layout that has

been experienced in many different ways across a multitude of episodes. However, when fine discrimination is needed to distinguish routes or landmarks from one another, perirhinal cortex may also play a role even for remote memories of those routes or landmarks (Burke et al., 2011). Our findings provide evidence that older adults benefit from spatial-relational cues that are extracted over many different encounters with an environment as they do from the semantic gist that is extracted over repeated and varied experiences.

ACKNOWLEDGMENTS

This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada and a Sloan Research Fellowship to R. Shayna Rosenbaum and Canadian Institutes of Health Research (Grant #: MGP 6694) to R. Shayna Rosenbaum, Gordon Winocur, and Morris Moscovitch. The authors gratefully acknowledge the technical assistance of Nicholas Hill, Janet Roberts, and Audrey Wong. We also thank Thomas Wolbers, Eric Blalock, and Sue Becker for their valuable comments.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 May 2012; accepted: 16 August 2012; published online: 13 September 2012.

*Citation: Rosenbaum RS, Winocur G, Binns MA and Moscovitch M (2012) Remote spatial memory in aging: all is not lost. Front. Ag. Neurosci. **4**:25. doi: 10.3389/fnagi.2012.00025*

frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 29 August 2012
doi: 10.3389/fnagi.2012.00024

Local amplification of glucocorticoids in the aging brain and impaired spatial memory

Joyce L. W. Yau* and Jonathan R. Seckl

Centre for Cognitive Ageing and Cognitive Epidemiology and Endocrinology Unit, Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Edited by:
Emma R. Wood, University of Edinburgh, UK

Reviewed by:
Jacques Micheau, University of Bordeaux 1, France
Eric Blalock, University of Kentucky, USA

****Correspondence:***
Joyce L. W. Yau, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ, UK.
e-mail: joyce.yau@ed.ac.uk

The hippocampus is a prime target for glucocorticoids (GCs) and a brain structure particularly vulnerable to aging. Prolonged exposure to excess GCs compromises hippocampal electrophysiology, structure, and function. Blood GC levels tend to increase with aging and correlate with impaired spatial memory in aging rodents and humans. The magnitude of GC action within tissues depends not only on levels of steroid hormone that enter the cells from the periphery and the density of intracellular receptors but also on the local metabolism of GCs by 11β-hydroxysteroid dehydrogenases (11β-HSD). The predominant isozyme in the adult brain, 11β-HSD1, locally regenerates active GCs from inert 11-keto forms thus amplifying GC levels within specific target cells including in the hippocampus and cortex. Aging associates with elevated hippocampal and neocortical 11β-HSD1 and impaired spatial learning while deficiency of 11β-HSD1 in knockout (KO) mice prevents the emergence of cognitive decline with age. Furthermore, short-term pharmacological inhibition of 11β-HSD1 in already aged mice reverses spatial memory impairments. Here, we review research findings that support a key role for GCs with special emphasis on their intracellular regulation by 11β-HSD1 in the emergence of spatial memory deficits with aging, and discuss the use of 11β-HSD1 inhibitors as a promising novel treatment in ameliorating/improving age-related memory impairments.

Keywords: corticosterone, cortisol, watermaze, hippocampus, 11β-HSD1, neurosteroids, CYP7B1

INTRODUCTION

Cognitive decline is a key feature of aging but significant impairments of learning and memory are not inevitable or strictly linked to chronological age. Marked inter-individual variability exists, ranging from almost no decline through mild impairments to frank dementia. This phenomenon has been described in several species including rodents and humans but the mechanisms underlying the individual differences remain poorly understood. One important mechanistic hypothesis is that variations in hypothalamic-pituitary-adrenal (HPA) activity and consequent exposure to glucocorticoids (GCs; cortisol in humans, corticosterone in rodents) during life may contribute to the inter-individual differences in cognitive decline in animals and humans.

The adrenal cortex synthesizes GCs and these steroid hormones are released directly into the peripheral circulation following stimulation of the HPA axis in response to external (stress) and internal (circadian) cues. Collectively, GCs released in coordination with the rapidly acting sympathetic-adrenomedullary system, help an organism respond to "stressors" or threats to homeostasis by mobilizing energy stores, suppressing nonessential physiological processes (e.g., reproduction, digestion) and initiating behavioral responses. Circulating GC levels are normally tightly regulated by negative feedback inhibition upon the HPA axis where GCs act back on the hypothalamus and pituitary glucocorticoid receptors (GRs) (to suppress CRH and ACTH production) to terminate its own release. GC feedback also occurs in higher centers such as the hippocampus and cingulate cortex.

GCs readily enter the brain, a major target for GC action (McEwen et al., 1968). Here GCs bind to classical nuclear (hormone) receptors to regulate the transcription of specific genes, either by direct binding of receptor homodimers to DNA (Datson et al., 2001) or via protein-protein interactions with other transcription factors such as fos and Jun-1 (Heck et al., 1994; Hayashi et al., 2004). Through activation of their intracellular receptors, GCs affect a wide range of processes including altering neurotransmission, electrophysiological activity, cellular metabolism, and structure, as well as neuronal division, maturation, and death.

CORTICOSTEROID RECEPTORS

Two types of corticosteroid receptors exist, the type I high affinity mineralocorticoid receptors (MR) and type II lower affinity GRs (Reul and de Kloet, 1985). Although sharing almost identical DNA-binding domains, MR and GR can exert distinct cellular functions as the genes they bind to show little overlap (Datson et al., 2001). GRs are widely distributed throughout the brain in most neurons and glia. GRs have a lower affinity for physiological GCs and only become substantially activated as hormone levels rise following stress. MR is expressed in neurons only and has a more restricted distribution with high expression confined particularly to the hippocampus (**Figure 1**), and septum. MRs having a 10-fold higher affinity for physiological

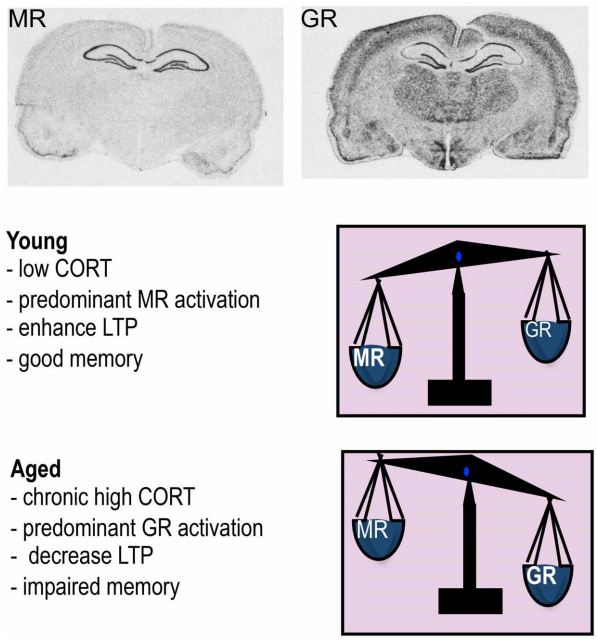

FIGURE 1 | Mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) mRNA expression in rat brain. The high affinity MR is predominantly occupied under low corticosterone (CORT) levels typically observed in young animals under basal conditions and this leads to enhanced LTP and good memory. When CORT levels rises such as in aging, MR is fully occupied and the excess GCs now occupy more GR so the balance of receptors activated is now predominantly GR which decreases LTP and impairs memory.

corticosteroids (GCs and the mineralocorticoid aldosterone) are extensively occupied under basal conditions when hormone levels are low (Reul and de Kloet, 1985; McEwen et al., 1986).

In addition to the delayed genomic effects via intracellular MR and GR, it has become evident from recent work that GCs also affect brain function through rapid non-genomic membrane-associated mechanisms (Groeneweg et al., 2011) (**Figure 2**). The latter mode of action explains the rapid (minutes) effects of GCs on the excitability and activation of neurons in several brain regions (e.g., hypothalamus, hippocampus, amygdala, and prefrontal cortex) and provides a physiological basis for rapid effects on behavior (de Kloet et al., 2008). A membrane-localized form of MR appears to mediate the rapid GC signaling in the hippocampus (Karst et al., 2005). However, not all rapid GC effects occur via MRs with some [e.g., increase in spine density of hippocampal neurons (Komatsuzaki et al., 2005)] depending on membrane-located GRs rather than MRs and others [e.g., long-term potentiation (LTP) induction (Wiegert et al., 2006), NMDA-dependent neurotoxicity (Xiao et al., 2010)] occurring independent of MR or GR but mediated possibly through as yet unidentified membrane-localized receptors.

BLOOD GLUCOCORTICOID LEVELS

Short term increases in GC levels are normally adaptive and beneficial but prolonged exposure to elevated GC levels such as during chronic stress or as a consequence of failure or impairment of negative feedback control of GC secretion (e.g., Cushing's syndrome, major depression) will lead to excessive GC responses and to pathology in the periphery (e.g., diabetes, hypertension, osteoporosis, central obesity) and CNS (e.g., depression, impaired learning, and memory). Cushing's syndrome patients with hyper-secretion of cortisol show reduced hippocampal volume and impaired performance on hippocampal learning tasks (Starkman et al., 1992). Notably, successful treatment to correct the excessive secretion of GCs reverses the pathology including hippocampal structural recovery and the restoration, to some extent, of mood, learning, and memory (Starkman et al., 1999). Conversely, severely reduced GC levels, as in Addison's disease, also result in pathology and cognitive impairments (Tytherleigh et al., 2004) and are treated with lifelong corticosteroid replacement. Thus both too little and too much GCs can have detrimental effects on memory, emphasizing the crucial need to maintain optimal levels of GCs for health and survival.

GLUCOCORTICOIDS AND HIPPOCAMPUS-DEPENDENT MEMORY

GCs via binding to abundant MRs and GRs in the hippocampus control the excitability of neuronal networks that underlie learning and memory processes. While not the focus of this review, it is worth noting that other brain areas rich in GRs such as the basolateral amygdala (BLA) and prefrontal cortex, which controls emotional and working memory respectively, interacts with the hippocampus to modulate cognitive function (Roozendaal and McGaugh, 1997, 2011). An efficient interplay between activation of MR and GR appears essential for maximal learning. The two receptors have different roles in learning as evident from rodent studies, especially in the watermaze using antagonists of MR and GR at the various phases of spatial learning (Oitzl and de Kloet, 1992); MRs have a major role in behavioral reactivity toward stimuli while GRs are involved in consolidating learned information. Furthermore, the ratio of occupation and presumably activation of MR/GR appears to determine whether GCs improve or impair memory (de Kloet et al., 1999). Thus, optimal enhanced memory occurs when GC levels are mildly elevated such that most MRs and only some GRs are activated (i.e., increased MR/GR ratio) but impaired memory results when circulating GC levels are greatly increased such as found in some aging individuals (i.e., low MR/GR ratio) (Kim and Diamond, 2002; Tytherleigh et al., 2004; Herbert et al., 2006) (**Figure 1**). Indeed, circulating basal (nadir) GC levels do not always increase as a function of chronological age with only a proportion of individuals showing increasingly high GC levels with advancing age while some show levels within the young normal range (Lupien et al., 1994).

MR AND GR ACTIVATION

Whether the consequence of the receptor activation is positive or negative for memory depend largely on the context of the situation/event to be remembered, the timing and the magnitude of the increased GC levels (de Kloet et al., 1999; Joels et al., 2006). Acute stress or increased GC levels occurring around the time of learning and within the context of the event to be remembered enhances memory consolidation. In contrast, they impair memory if occurring either before or a considerable time

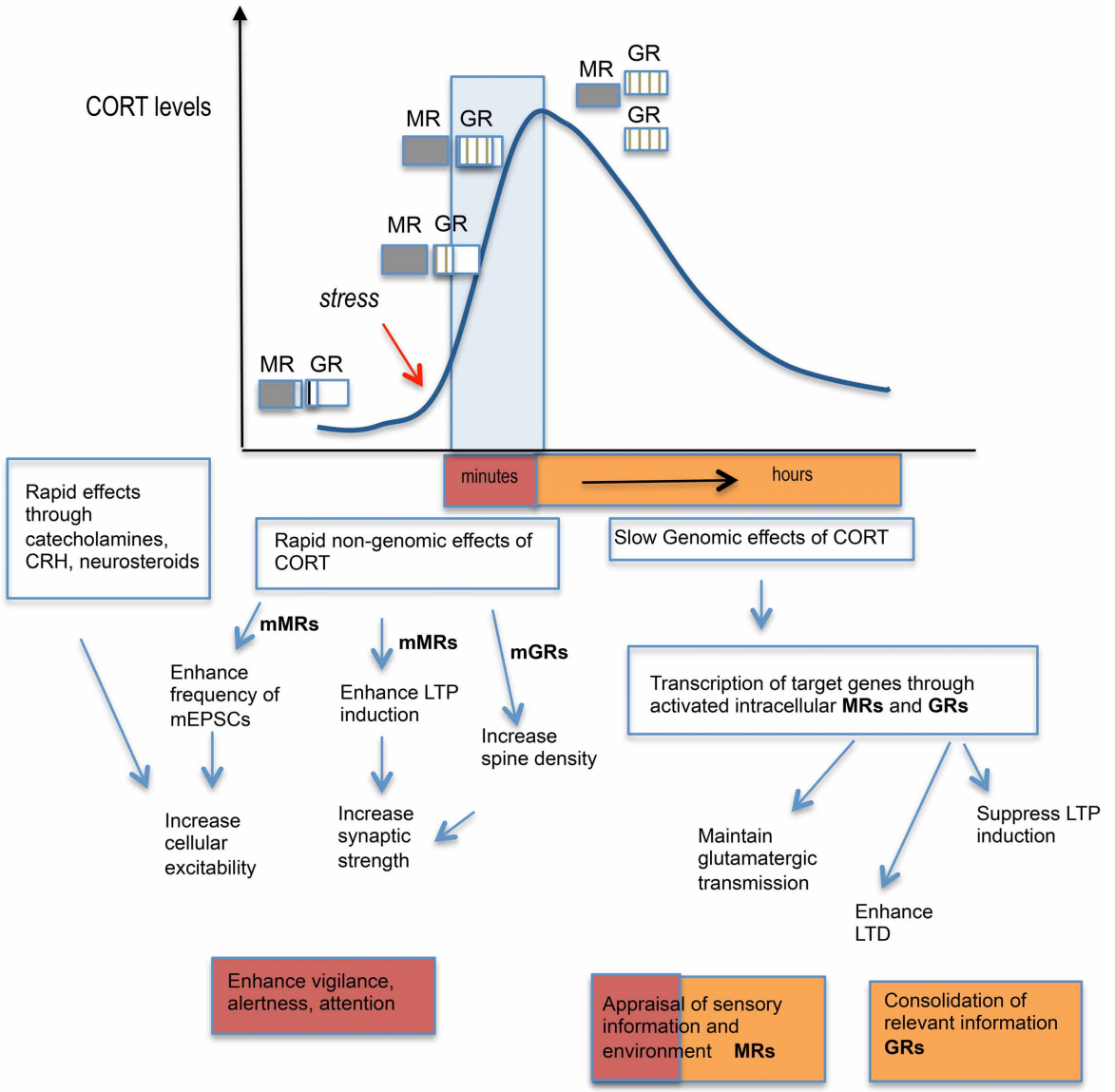

FIGURE 2 | Schematic diagram showing stress hormone effects: from cellular responses to behavior. Activation of the HPA axis by stress leads to a rapid rise in circulating corticosterone (CORT) levels which starts to fully occupy MR and increasingly occupy GRs. The varying level of occupancy of MRs and GRs are represented by extent of shading or lines within the boxes. The CORT levels normally return to baseline levels by 2 h through negative feedback regulation upon the HPA axis. The initial rapid effects of CORT via activation of membrane-located MRs enhance LTP induction and enhance miniature excitatory postsynaptic currents in the hippocampus while membrane-located GRs appear to increase neuronal spine density. Together with other stress hormones released such as the catecholamines (noradrenaline and adrenaline) and corticotropin-releasing hormone (CRH), which also strengthen synaptic transmission in the hippocampus, these rapid events contribute to enhanced vigilance, alertness, and attention. The slower genomic effects of CORT through activation of intracellular MRs and GRs and the transcription of target genes, leads to the maintenance of glutamatergic transmission via MRs and suppression of LTP induction but enhanced LTD via GRs in the hippocampus. MRs and GRs contributes to different aspects of cognitive processing with MR activation responsible for the appraisal of sensory information and environmental cues, while GRs are important for the consolidation of events/information in memory.

after the learning task (Quervain et al., 1998; Cazakoff et al., 2010). Evidence, mainly from animal studies, suggests that GCs preferentially enhances memory consolidation of emotionally arousing experiences (Roozendaal et al., 2006). Animal learning tasks, including the Morris watermaze and radial arm maze for spatial memory training, are designed to be generally affectively arousing because they require motivation to elicit changes in behavior. Even learning tasks that include no rewarding or aversive stimulation, such as the object recognition task, induces modest novelty-induced stress or arousal during training (Okuda et al., 2004). GCs released during learning appear essential for establishing enduring memories (De Kloet et al., 1998). Thus,

small increases in GCs enhance hippocampus-mediated learning and memory while larger, prolonged elevations impair memory (Lupien and McEwen, 1997; Kim and Diamond, 2002). This follows the inverted U-shaped dose-response relationship between GC levels and effects on hippocampal LTP, an electrophysiological phenomenon associated with synaptic strengthening which is one of the major cellular mechanisms underlying learning and memory. Low moderate GC levels occupy predominantly high affinity MR which increases LTP and memory, while high GC levels occupy the lower affinity GR (in addition to MR) and impair LTP and memory (Pavlides et al., 1995, 1996; Kim and Diamond, 2002; Kim et al., 2007). One recent study supports the inverted-U-shaped relationship between intrinsic stress intensity (i.e., increased endogenous GCs induced by factors associated with the learning task, in this case water temperature) and spatial memory in the radial arm watermaze. Thus, rats trained at 19°C made fewer errors than rats trained at either more (16°C) or less (25°C) stressful conditions (Salehi et al., 2010).

THE AGING HIPPOCAMPUS

The hippocampus not only plays a central role in the processing of spatial and contextual information (Morris et al., 1982; Moser et al., 1995) but also exerts an inhibitory influence over HPA function (Jacobson and Sapolsky, 1991). With its high density of MRs and GRs, the hippocampus is also particularly sensitive to the deleterious actions of chronic GC excess, potentiating neurotoxicity, dendritic atrophy, and perhaps even neuronal loss (Sapolsky, 1987). The idea that excess GCs could promote aging of the hippocampus was first established over 30 years ago following a study that showed a positive correlation between hippocampal aging (astrocyte reactivity as a marker of neuronal damage) and plasma levels of corticosterone in aging rats (Landfield et al., 1978). While only a few studies have shown high GC levels or stress actually cause hippocampal neuron loss (Uno et al., 1989; Sousa et al., 1998), much evidence support chronic stress (or high GCs) causing hippocampal atrophy (Watanabe et al., 1992; Magarinos and McEwen, 1995).

In humans, including those with Cushing's disease, Alzheimer's disease, depression, and normal aging, higher cortisol levels have been associated with poorer memory and hippocampal shrinkage/neuronal loss (De Leon et al., 1988; Wolkowitz et al., 1990; Newcomer et al., 1994; Mitchell and Dening, 1996; Lupien et al., 1998; Karlamangla et al., 2005; MacLullich et al., 2005). Moreover, increased HPA activity, as a consequence of impaired HPA axis negative feedback control, has been hypothesized to contribute to the decline in cognitive function, including deficits on spatial tasks with aging (Ohta, 1981; Lupien et al., 1998; McEwen et al., 1999). In support, the extent of age-related cognitive impairments in rodents and humans correlates with increased HPA activity (Issa et al., 1990; Meaney et al., 1995; Yau et al., 1995; Lupien et al., 1996, 1998). Aging rodents also show difficulty with hippocampus-dependent tasks that require a spatial mapping strategy; acquisition deficits have been reported in spatial information processing tests including Barnes hole-board task, radial arm mazes, and Morris watermaze (Ingram et al., 1981; Barnes and McNaughton, 1985; Gage et al., 1989; Issa et al., 1990; Gallagher et al., 1993; Yau et al., 1994, 1995).

GLUCOCORTICOIDS AND OTHER BRAIN SITES

Although GCs act on the hippocampus to modulate the formation of new memories, it also acts at other sites, notably the amygdala and prefrontal cortex, which functionally interact. Thus, GC effects on hippocampal LTP and memory can be blocked by lesions to the BLA (Roozendaal and McGaugh, 1997; Kim et al., 2001) and much evidence supports a role of the BLA via emotional arousal-induced noradrenergic activation and GR actions in the modulation of memory consolidation and working memory (Roozendaal and McGaugh, 2011). Given that amygdala function is affected by aging (Iidaka et al., 2002; Charles et al., 2003), it might be expected that fear conditioning would also be disrupted with aging and hence influence hippocampal memory deficits. However, age-related impairments in spatial memory appear not to be influenced by emotional and contextual memories, which tend to be preserved with aging (Comblain et al., 2004; Gould and Feiro, 2005; May et al., 2005; Bergado et al., 2011; Broster et al., 2012).

GLUCOCORTICOIDS AND INTER-INDIVIDUAL DIFFERENCES IN SPATIAL MEMORY

AGED RATS

As a group, aged rats show impaired spatial learning. However, there are substantial inter-individual differences in performance (Yau et al., 1995). This increased variation in aged rats allows subdivision into categories (cognitively-unimpaired, cognitively-impaired) in the watermaze according to their latency to find the submerged platform on the last days of training relative to the mean latency of young controls (Issa et al., 1990; Tombaugh et al., 2002) or to a learning index score computed from probe trials (during retraction of the platform to the bottom of the pool during 30 s of 90 s trials) (Gallagher et al., 1993; Wilson et al., 2004; Robitsek et al., 2008). Aged rats have also been subdivided into impaired and unimpaired categories according to their spatial memory performance in a Y-maze two-trial spatial recognition task where the mean value of the percentage of visits in the novel arm of impaired rats were not different from chance values (Vallee et al., 1997). We typically find approximately ∼20–25% of aged Lister hooded rat cohorts differ significantly (>2.5 SD) from young controls in the watermaze (escape latency and probe times) and another ∼20–25% not significantly different (<0.5 SD) from young controls (**Figure 3**). It is the cognitively impaired groups that selectively show elevated plasma corticosterone levels (Issa et al., 1990; Yau et al., 1995), and reduced hippocampal corticosteroid receptor density (Issa et al., 1990; Yau et al., 1995) compared to both young and similarly aged cognitively unimpaired rats (Issa et al., 1990). While aged rats with watermaze performances not significantly different from young rats have been sub-classed as "cognitively unimpaired," it is important to note that they are not cognitively the same as young rats. Indeed, we found that aged Lister hooded rats, categorized as unimpaired by their performance in the conventional spatial memory watermaze task, were impaired in a more cognitively demanding delayed matching-to-place paradigm spatial memory watermaze task (Steele and Morris, 1999) when compared to young controls (Yau and Seckl, unpublished).

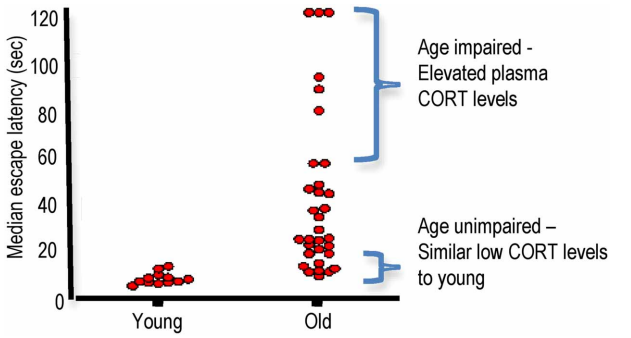

FIGURE 3 | Aged Lister hooded rats show inter-individual differences in spatial learning in the watermaze. 24 months old male Lister hooded rats show impaired spatial learning and memory in the watermaze as a group compared to 6 months old controls. However, individual performances taking the median of the escape latencies (4 trials/day) for the last 2 days of training shows a large spread of learning abilities for aged rats. Plasma corticosterone (CORT) levels in the aged rats correlated negatively with spatial memory with impaired aged rats showing increased CORT while unimpaired aged rats had lower CORT similar to young controls (Based on Yau et al., 1995, with permission from Elsevier).

AGED MICE

Aged mice also show impaired spatial memory in the watermaze (Verbitsky et al., 2004; Pawlowski et al., 2009) and increased plasma CORT levels (Yau et al., 2001, 2007; Holmes et al., 2010) such that higher CORT levels correlates with impaired learning in the watermaze (Yau et al., 2001). However, in contrast to aged rats, subdividing aged mice cohorts into cognitively aged-impaired and aged-unimpaired groups is less clear-cut with large variations in performance found even in young controls (Pawlowski et al., 2009). Mice in general take longer to train in the watermaze than rats and show less consistent performance with some aged mice tending to float rather than swim. The Y-maze spatial recognition task, in contrast to the watermaze, is an ethologically relevant test based on the rodent's innate curiosity to explore novel areas and presents no negative or positive reinforcers and little stress for the rodents. When spatial memory was tested in the Y-maze using a 2 h inter-trial interval, young C57BL/6J mice can still remember the novel arm (exploring it more than the other two arms) while aged mice were overall impaired as a group (not distinguishing the novel arm between the three arms). As in the watermaze, inter-individual differences in Y-maze spatial memory performances exist in aged mice, but with a smaller percentage of aged mice "unimpaired" (<20%) while the majority were "impaired" (Yau and Seckl, unpublished).

GLUCOCORTICOIDS AND MAINTAINENCE OF SPATIAL MEMORY WITH AGING

In rats, manipulations which keep GC levels low throughout life, such as postnatal handling during the first two weeks of life (which permanently increases hippocampal expression of GR, thus improving HPA axis negative feedback to reduce circulating GC levels), denser maternal care (licking and arched back nursing of her offspring), or adrenalectomy at middle age with low dose corticosterone replacement, prevent later hippocampal morphological changes and spatial memory deficits with aging (Landfield et al., 1981; Meaney et al., 1988). Although such manipulations are probably not clinically utilizable, they suggest that pharmacological treatments to increase GR density in the adult hippocampus may reduce GC levels long-term and ameliorate or prevent the emergence of spatial memory impairments with aging. One potent long-term regulator of MR and GR in the hippocampus is serotonin; this neurotransmitter directly increases GR in primary neuronal cultures and *in vivo* following postnatal handling of rat pups (Mitchell et al., 1990; Meaney et al., 1994; Lai et al., 2003) while lesions of the serotonergic pathway reduces hippocampal MR and GR (Yau et al., 1997). Antidepressants, which amongst other effects, increases serotonin levels, increase hippocampal GR density, improve HPA feedback regulation and thus reduce GC levels in adult rats and mice (Reul et al., 1993; Montkowski et al., 1995; Barden, 1996). Chronic (2 months) treatment of aged Lister hooded rats with amitriptyline, however, did not prevent spatial memory impairments but treatment of young (8 months) animals improved spatial memory, reduced plasma corticosterone levels, and increased hippocampal MR mRNA expression (Yau et al., 1995). Since hippocampal MR enhances LTP (Pavlides et al., 1994) and has a positive influence on memory while central MR blockade impairs spatial memory in adult rats (Yau et al., 1999), the antidepressant induced increase in hippocampal MR may, in part, underlie the better spatial memory in the young rats. Aged rats may lack the plasticity for antidepressants to be effective at enhancing memory later in life. In support, earlier treatment with antidepressants from middle age (for 6 months) improved HPA negative feedback (Rowe et al., 1997) and reduced the emergence of spatial memory impairments in a cohort of aged rats (Yau et al., 2002).

TISSUE SELECTIVE REGULATION OF GLUCOCORTICOID EXPOSURE

While many studies have measured blood GC levels and correlated this to GC actions within tissues of interest, the principal determinant of GC action is the level of hormone inside the cell. The magnitude of intracellular GC action has long been thought to be determined by the concentration of active hormone in the circulation [modulated by hormone binding to plasma proteins, mainly corticosteroid binding globulin (CBG)] and the density of intracellular receptors in target tissues. However, during the past two decades, enzymic pre-receptor metabolism of GCs by 11β-hydroxysteroid dehydrogenases (11β-HSDs) has emerged as a key mechanism for tissue specific control of active GC levels (Seckl, 1997). 11β-HSDs are microsomal (endoplasmic reticulum) enzymes which catalyse the interconversion of active GCs (corticosterone in rodents, cortisol in humans) and inert 11-keto forms [11-dehydrocorticosterone (11-DHC), cortisone]. They thus, potently regulate steroid access to receptors within specific tissues (Seckl, 1997).

11β-HYDROXYSTEROID DEHYDROGENASE TYPE 1

11β-HSD1 is the predominant isoform in the adult rodent and human brain, where it is widely distributed with particularly

high expression in the hippocampus, cerebellum, and cortex in both neurons and glia cells (Moisan et al., 1990; Sandeep et al., 2004). 11β-HSD2 whilst highly expressed in the fetal CNS until mid-gestation, in the adult brain is restricted to the nucleus of the solitary tract (NTS) in mice and this plus a few other scattered brain stem and diencephalic nuclei in rats. 11β-HSD2 acts as a dehydrogenase to inactivate GCs before they can bind to receptors. It is best noted for its role to exclude GCs from otherwise non-selective MRs in the distal nephron, thus allowing aldosterone selectivity. 11β-HSD1 in contrast functions as a 11β-reductase (regenerating active GCs from inert 11-DHC) in intact cells, thus locally "amplifying" GC levels within brain cells as well as in liver, adipose tissue, immune system cells etc (**Figure 4**). This direction of action, far from protecting neurons against GC excess, would be anticipated to increase local intraneuronal GC levels, potentiating their effects including toxicity. Consistent with this hypothesis, *in vitro* otherwise inert 11-DHC potentiates kainate neurotoxicity in hippocampal cells in culture, as a consequence of its conversion to active corticosterone by 11β-HSD1 expressed in the neurons, an effect lost in the presence of an 11β-HSD inhibitor (Rajan et al., 1996). The importance of such regeneration of GCs within cells *in vivo* was shown in mice homozygous for targeted disruption of the 11β-HSD1 gene (Kotelevtsev et al., 1997). 11β-HSD1 appears to be the only 11β-reductase, at least in mice, since knockout (KO) animals cannot convert 11-DHC to active corticosterone and showed evidence of reduced tissue GC actions (e.g., resist hyperglycaemia induced by obesity or stress) (Kotelevtsev et al., 1997). So are there brain effects of 11β-HSD1 deficiency?

11β-HSD1 AND HPA AXIS ACTIVITY

Expression of 11β-HSD1 in brain sites (prefrontal cortex, hippocampus, hypothalamus) and pituitary that underpin negative feedback actions of GCs suggests that this enzyme may influence HPA axis activity. In order to maintain tissue GC levels in feedback sites that normally express 11β-HSD1, higher levels of plasma GCs would be predicted to result as a consequence of loss of local production of active GCs at these sites. Indeed mice lacking 11β-HSD1 on the 129/MF1 strain showed evidence of reduced HPA axis feedback sensitivity (elevated nadir levels of plasma corticosterone, enlarged adrenal glands, and exaggerated GC response to an acute stressor) (Harris et al., 2001). However,

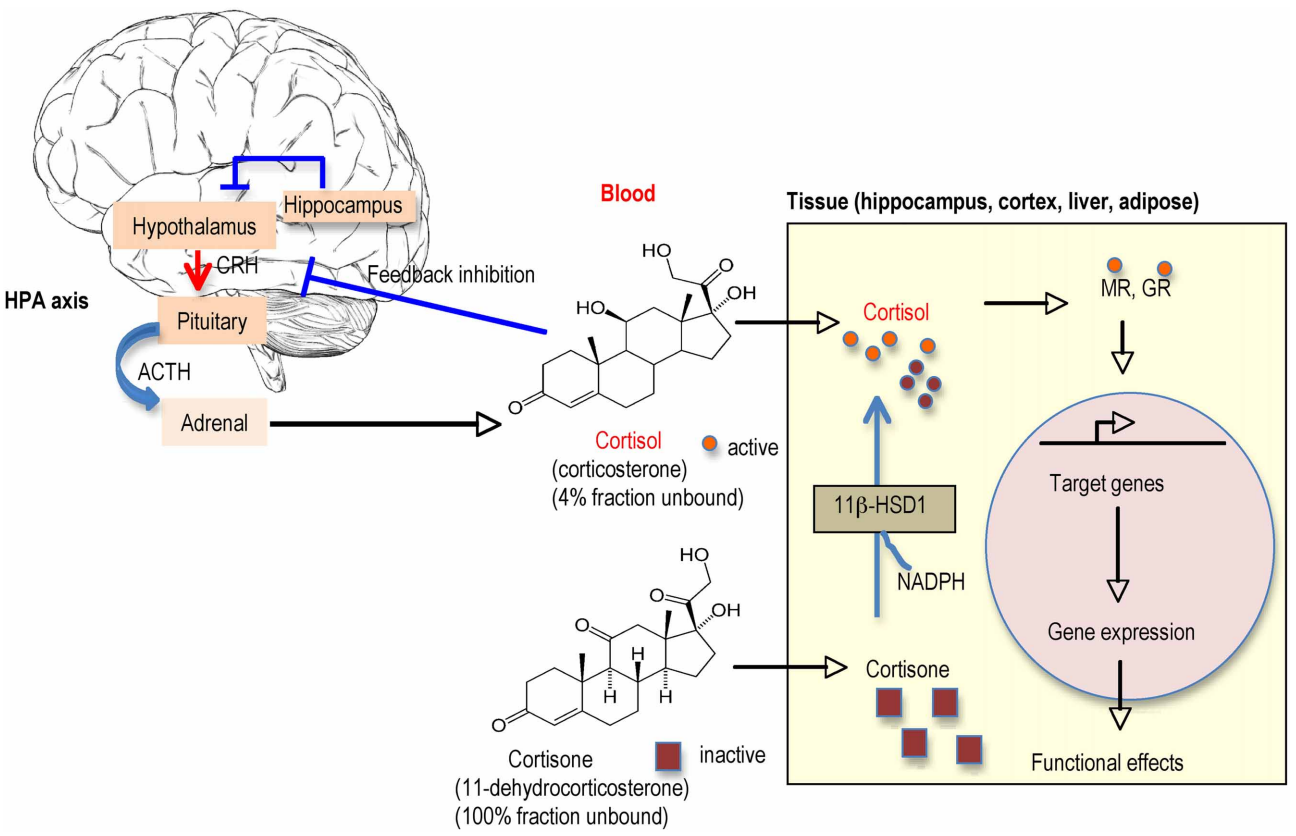

FIGURE 4 | Regulation of glucocorticoid (GC) levels in blood and tissues. Circulating GC levels are tightly regulated by negative feedback inhibition at the hypothalamic-pituitary-adrenal (HPA) axis. Active GCs (cortisol in humans, corticosterone in rodents) circulate mostly bound to CBG (corticosteroid binding globulin) such that only ~4% are free to enter tissues. The inactive GCs (cortisone, 11-dehydrocorticosterone) the products of 11β-HSD2 metabolism mainly in kidney, circulates unbound to plasma proteins so all are available to enter tissues. Once inside the cell, there is another level of control by the presence of 11β-HSD1 (found in specific cells in the adult brain such as in hippocampus and cortex and other tissues such as liver and adipose). 11β-HSD1 regenerates active GCs from their inactive forms thereby effectively amplifying intracellular GC levels before they bind to MR and/or GR (depending on brain region). The activated receptors then translocate into the nucleus to activate the transcription of target genes.

the effects of 11ß-HSD1 deficiency on HPA axis activity were lost when the mice were bred onto another genetic background strain. Thus, 11β-HSD1 KO mice congenic on a C57BL/6J background show normal nadir plasma corticosterone levels and efficient negative feedback regulation thought to be due to compensatory increased GR expression in the hippocampus and paraventricular nucleus of the hypothalamus (Carter et al., 2009). Activation of the HPA axis is therefore not an inevitable consequence of 11β-HSD1 deficiency or inhibition. The genetic background appears crucial in governing the HPA axis response to 11β-HSD1 deficiency or inhibition.

IMPLICATIONS OF 11β-HSD1 FUNCTION IN THE AGING BRAIN

If 11β-HSD1 locally regenerates active GCs thus amplifying GC action within specific cells *in vivo*, this direction of enzyme activity would be anticipated to impair spatial memory in the aging brain when there is the additional contribution of increased "free" unbound GCs from the periphery in individuals with elevated blood GC levels. Indeed, a lack of the enzyme in the aged brain appears beneficial to memory processes as shown in 11β-HSD1 KO mice (Yau et al., 2001). Thus, aged 11β-HSD1 KO mice congenic on the 129 strain, despite modestly elevated plasma corticosterone levels throughout life, show ameliorated GC-related learning impairments in the watermaze (Yau et al., 2001). *This is the opposite of what would be anticipated if only circulating corticosterone levels were taken into consideration*. Hippocampal tissue corticosterone levels measured *ex-vivo* were significantly lower in aged 11β-HSD1 KO mice than aged controls (Yau et al., 2001, 2011), supporting the important role the enzyme plays in determining the levels of GCs within cells and thus their action.

AGED 11β-HSD1 KNOCKOUT MICE

Different genetic background mouse strains can exhibit marked differences in learning and memory (Owen et al., 1997). The original 11β-HSD1 KO mice generated on the 129 Ola background learnt a cued version of a watermaze task (Yau et al., 2001), but had difficulty learning the classical task. Subsequently, aged 11β-HSD1 KO mice congenic on the C57BL/6J background, the strain of choice in many behavioral tests, also showed an improved cognitive phenotype resisting the spatial memory impairments observed in many aged control mice, this time observed in the standard reference memory watermaze and also Y-maze spatial recognition tasks (Yau et al., 2007). Even a 50% reduction in 11β-HSD1 in heterozygous 11β-HSD1 KOs is enough to prevent age-related spatial memory impairments (Sooy et al., 2010).

INCREASED HIPPOCAMPAL 11β-HSD1 AND IMPAIRED SPATIAL MEMORY

Aged C57BL/6J mice showed increased 11β-HSD1 expression in the cortex (layer V) and CA3 cells of the hippocampus compared to young controls. Moreover, hippocampal and cortical 11β-HSD1 mRNA levels correlate with impaired spatial learning in the watermaze (Holmes et al., 2010). The selective increase of 11β-HSD1 in the CA3 subregion of the memory-impaired hippocampus may be of functional significance since it is the CA3 cells that undergo dendritic atrophy following chronic restraint stress or corticosterone injections (Magarinos and McEwen, 1995), both of which impair spatial memory (Luine et al., 1994; Conrad et al., 1996; Wright and Conrad, 2005; Hoffman et al., 2011). CA3 appears crucial for memory acquisition and consolidation in the watermaze (Florian and Roullet, 2004). Furthermore, CA3 cells selectively fail to rapidly encode new spatial information in memory-impaired aged rats (Wilson et al., 2005). This suggests that the implied increase of GC levels driven by variable overexpression of 11β-HSD1 in CA3 of aged mice may be a major contributor to the spatial memory deficits with aging. The mechanisms underlying the upregulation of 11β-HSD1 in CA3 and cortex of aged mice are unknown. GCs and stress elevate hippocampal 11β-HSD1 in young animals affording a possible feed-forward system to amplify GC action (Low et al., 1994). Consistent with increased 11β-HSD1 levels in the hippocampus impairing memory with aging, transgenic mice overexpressing 11β-HSD1 in the forebrain under the CAMIIK promoter resulting in 50% increase in the hippocampus, developed premature memory impairments with deficits in hippocampus-dependent learning tasks (watermaze spatial reference memory and passive avoidance memory) at 18 months (Holmes et al., 2010).

HIPPOCAMPAL PLASTICITY AND AGING

LTP AND LTD

In the absence of hippocampal neuron loss, age-related spatial learning deficits in rats may be the result of more subtle changes in synaptic structure or function (Rapp and Gallagher, 1996; Smith et al., 2000). Consistent with this idea, impaired hippocampal synaptic plasticity, specifically LTP in aged rats relates to individual differences in spatial learning ability (Deupree et al., 1991; Bach et al., 1999). Indeed, LTP induced in the CA1 region using theta-frequency stimulation (5 Hz) was selectively impaired in hippocampal slices from a subpopulation of aged rats that had previously shown poor spatial learning in the water maze (Tombaugh et al., 2002). Elevated corticosterone levels (presumably occupying both MR and GR) also impairs Primed Burst Potentiation (PBP), a low threshold form of LTP, in the hippocampal CA1 in the rat, while low levels of corticosterone (that would occupy mostly MRs) facilitates PBP (Diamond et al., 1992). Although the involvement of other hormones and/or brain regions may also play a role, high levels of corticosterone directly impairs hippocampal synaptic potentiation (Alfarez et al., 2002). In addition, induction of long-term depression (LTD), which in contrast to LTP weakens rather than strengthens synaptic contacts by repeated stimulation (Bear and Malenka, 1994), is enhanced by high corticosterone levels (Coussens et al., 1997) and during aging (Norris et al., 1996, 1998).

PRIMED BURST POTENTIATION

Primed burst stimulation induces lower potentiation in the hippocampus of young animals compared to the LTP induction protocol (Diamond et al., 1994, 1996; Alfarez et al., 2002), but few reports have shown this reliably in aged animals (Moore et al., 1993). We found very little PBP (a single

200 Hz stimulus followed 180 ms later by a burst of four stimuli at 200 Hz) in hippocampal slices from either 25 months old 11β-HSD1 KO or age matched controls. However, LTP induced with a single 100 Hz tetanus, was increased in hippocampal slices from aged 11β-HSD1 KO mice compared to aged-matched C57BL/6J controls (Yau et al., 2007). Thus, an increase in LTP in the hippocampus of aged 11β-HSD1 KO mice may, in part, underlie their retention of spatial memory with age.

GLUCOCORTICOIDS, NEUROGENESIS, AND AGING

Adult neurogenesis, the generation of new neurons via mitotic cell division, occurs in the dendate gyrus of the hippocampus throughout life. Although the full functional significance of these new neurons is not fully understood, there is increasing evidence to support the notion that these newborn neurons can mature, form synapses, integrate with the local circuitry, and are involved in hippocampus-dependent learning (Lemaire et al., 2012; Marin-Burgin and Schinder, 2012). Of relevance to aging, high levels of GCs or stress reduce neurogenesis (Czeh et al., 2002; Wong and Herbert, 2006). Indeed, neurogenesis is substantially reduced with aging in rodents (Seki and Arai, 1995; Kuhn et al., 1996) and this may be in part related to increased GC levels since within a cohort of aged rats, those with the highest GC levels had the lowest levels of neurogenesis (Montaron et al., 2006). Furthermore, when aged rats were subdivided into aged unimpaired and aged impaired according to their spatial learning abilities (the top and bottom 30% of the population), cell proliferation in the granule cell layer of the dentate gyrus correlated with spatial memory performances (Drapeau et al., 2003). However, when neurogenesis was examined in the aged 11β-HSD1 KO, there was no significant difference compared to aged C57BL/6J controls, although an increase in neurogenesis was observed in young 11β-HSD1 KO mice (Yau et al., 2007). This suggests that the maintained spatial memory in the aged 11β-HSD1 KO mice is not a consequence of increased neurogenesis and that reduced intrahippocampal GCs is insufficient to overcome the other factors linked with aging (e.g., decreased serotonin) that regulate neurogenesis.

11β-HSD1 INHIBITORS AND MAINTENANCE OF SPATIAL MEMORY WITH AGING

Since aged mice with complete or partial 11β-HSD1 deficiency throughout life are protected from spatial memory impairments (Yau et al., 2007; Sooy et al., 2010), inhibiting 11β-HSD1 activity might benefit cognitive function in the aging brain. The big question is can short-term pharmacological inhibition of 11β-HSD1 have memory-enhancing effects in aged rodents and humans? *In vivo* studies in humans are hampered by the non-selectivity of the originally available liquorice-based inhibitors. Carbenoxolone, an old drug formerly used clinically to treat peptic ulcers, inhibits both 11β-HSD1 and 11β-HSD2. This may not matter in the adult brain as the predominant isozyme is 11β-HSD1. Initial small exploratory studies, albeit randomized, double-blind, and placebo-controlled in healthy elderly men and middle-aged patients with type 2 diabetes (52–75 years) showed that carbenoxolone improved aspects of cognitive function (verbal fluency and verbal memory) after 4–6 weeks treatment (Sandeep et al., 2004). Note that amilioride was also given to prevent renal mineralocorticoid excess and hence hypertension. This gave the first indication that inhibition of 11β-HSD1 (assuming the effects were centrally mediated) may be a promising new approach to prevent/ameliorate cognitive decline in humans.

SELECTIVE 11β-HSD1 INHIBITION

Selective 11β-HSD1 inhibitors that can cross the blood brain barrier have recently been developed (Webster et al., 2007). Two weeks peripheral treatment with a CNS active selective 11β-HSD1 inhibitor (UE1961) in aged C57BL/6J mice improved spatial memory in the Y-maze compared to vehicle treated age-matched controls (Sooy et al., 2010). Moreover, intracerebroventricular administration of another selective 11β-HSD1 inhibitor (UE2316) for 2 weeks also reversed spatial memory impairments in aged C57BL/6J mice confirming mediation by brain 11β-HSD1 inhibition (Yau et al., unpublished). Thus, spatial memory impairments in aged mice are not always a consequence of irreversible brain structural changes and the effects of the inhibitor are most likely the consequence of reduced intracellular GC levels during spatial learning and recall. Previous studies have shown that it is the consequence of increased GCs as a result of hippocampal structural changes (e.g., chronic stress-induced dendritic atrophy) impairing HPA axis feedback that has the more important influence on spatial memory performance since such impairments can be prevented on the day of testing by blocking GC synthesis (Roozendaal et al., 2001; Wright et al., 2006).

OTHER POTENTIAL EFFECTS OF 11β-HSD1 INHIBITORS

Depending on the duration of treatment, selective 11β-HSD1 inhibitors may result in resistance of target tissues to GCs, including HPA axis regulatory centers of the brain and pituitary. This could lead to compensatory activation of the HPA axis in an attempt to compensate for the GC deficiency in negative feedback loci expressing 11β-HSD1 in a similar manner to that observed in 11β-HSD1 KO mice on the 129 genetic background (Harris et al., 2001). A hyperactive HPA axis would lead not only to excess plasma cortisol, but perhaps also to excess mineralocorticoid precursors (corticosterone and deoxycorticosterone) and androgens, all of which may manifest as unwanted side effects, such as hypertension and hirsutism/hyperandrogenization in women. The degree of HPA axis activation may depend on the genetic background of the individual, as in mice, as well as the levels of 11β-HSD1 in these tissues, which may differ under various environmental conditions (e.g., with stress, diet, aging). There is also the question of whether inhibition of 11β-HSD1 will affect other types of memory other than spatial memory in cognitively impaired aged individuals. In particular, emotional and fear associated memories, involving the basolateral amygdala, are known to be enhanced with increased GCs (Roozendaal and McGaugh, 2011). Hence, 11β-HSD1 inhibitors may compromise the strength of such memories but whether this is the case remains to be determined.

MAINTENANCE OF SPATIAL MEMORY WITH AGING VIA PREDOMINANT MR ACTIVATION

Impaired spatial memory in aged C57BL/6J mice correlates with higher plasma GCs which are thought to activate the lower affinity GR. Indeed central blockade of GR (but not MR) for 2 weeks reversed the impaired spatial memory in aged C57BL/6J mice in the Y-maze (Yau et al., 2011). This again suggests that the impaired memory in aged C57BL/6J mice is not a direct consequence of irreversible structural changes. The improved spatial memory in aged 11β-HSD1 KO mice has been proposed to occur via reduced intracellular GC levels altering the balance of receptor activation in favor of MR activation. In support, central blockade of MR but not GR in aged 11β-HSD1 KO mice reversed their improved spatial memory phenotype such that they were now impaired in the Y-maze (Yau et al., 2011). Therefore, decreasing GR/increasing MR activation appears effective at preventing spatial memory impairments even in already aged mice. Reducing GC action by altering the receptor balance from predominant GR activation to predominant MR activation may be achieved by the use of selective 11β-HSD1 inhibitors or GR antagonists. Long-term treatment with GR antagonists in humans, however, may potentially cause compensatory activation of the HPA axis to overcome the blockade thus producing generalized GC resistance (Bamberger and Chrousos, 1995). While the use of selective 11β-HSD1 inhibitors causes compensatory activation of the HPA axis simply to accommodate the reduced regeneration of GCs, elevation of cortisol levels was not observed with carbenoxolone in elderly humans (Sandeep et al., 2004) or with selective 11β-HSD1 inhibitors in clinical trials (Rosenstock et al., 2010). Similarly, corticosterone levels were not increased in aged C57BL/6J mice treated short-term with a selective 11β-HSD1 inhibitor (Sooy et al., 2010).

LINKS BETWEEN COGNITION AND GLUCOSE METABOLISM

GCs play a role in the regulation of peripheral glucose mobilization and metabolism. Much less is known about the effects of GCs on glucose metabolism in brain tissues. GCs inhibit glucose utilization in the hippocampus (Sapolsky, 1986). Adrenalectomy decreases serum glucose levels and increases hippocampal glucose utilization (Kadekaro et al., 1988). While exogenously administered GCs adversely affect human memory consolidation and recall (Newcomer et al., 1994), glucose improves memory performance in normal elderly individuals (Hall et al., 1989) and in subjects with probable Alzheimer's disease (Craft et al., 1993). Studies in rodents suggest that hyperglycemia and high-fat diets adversely affect hippocampal function (Kamal et al., 2000; Molteni et al., 2002). In humans, hyperglycemia associate with decline in cognitive function with aging (Convit et al., 2003). Since 11β-HSD1 KO mice lack the enzyme in all tissues, it is possible that the cognitive protection in aged 11β-HSD1 KO mice may reflect, in part, their improved metabolic profiles (Kotelevtsev et al., 1997; Morton et al., 2001), rather than solely the direct effects of enzyme deficiency in the brain. However, aged 11β-HSD1 KO mice show no significant difference in glucose tolerance compared to age-matched controls (Yau et al., 2007). Moreover, the 11β-HSD inhibitor carbenoxolone improved cognitive function in aged humans without altering plasma glucose levels (Sandeep et al., 2004). Thus, the implication is that direct CNS effects of 11β-HSD1 deficiency or inhibition are more likely responsible for the observed improved cognitive function.

HIPPOCAMPAL GENE EXPRESSION ASSOCIATED WITH 11β-HSD1 DEFICIENCY AND MAINTENANCE OF SPATIAL MEMORY WITH AGING

To further our understanding of how GC action affects age-related memory performance, it will be important to determine the downstream genes/pathways activated by hippocampal MR and GRs that leads to the impaired and improved spatial memory of aged mice with and without 11β-HSD1. Several studies have examined hippocampal gene expression changes associated with age-related cognitive decline in rats and mice (Burger et al., 2007; Rowe et al., 2007; Pawlowski et al., 2009). Using microarrays, many hippocampal genes were found to be altered with aging regardless of cognitive status. Down-regulated genes in rat hippocampus are involved in mitochrondrial function, cell signaling, neural plasticity, and synaptic function whereas up-regulated genes underpin inflammation, glial structure, cholesterol transport, and lipid/protein degradation. Genes selectively downregulated in spatial memory impaired aged rats characterized in the watermaze and culled soon after training include a number of immediate early genes (IEGs) such as *Arc and Zif268* (also called *Egr-1* and *NGFI-A*) and glucose ultilization/insulin signaling genes such as *Irs1, GcK,* and *Insr* (Rowe et al., 2007). *Zif268,* is thought to activate the transcription of genes essential for hippocampus-dependent long-term memory (Jones et al., 2001). Reduced resting levels of *Zif268* mRNA in the CA1 hippocampal area of aged rats with impaired spatial learning have been observed by microarray analysis and in situ hybridization histochemistry (Yau et al., 1996; Blalock et al., 2003). Whether the selective alterations in gene transcription in cognitively impaired but not unimpaired aged animals is related to their HPA activity and hence circulating GC levels is not known. Hippocampal gene expression microarrays and proteomic approaches in behaviorally defined aged mice including aged 11β-HSD1 KO mice and animals given selective 11β-HSD1 inhibitors may indicate new drug targets for the enhancement of memory in the aged individual.

NEUROSTEROIDS, CYP7B1, AND SPATIAL MEMORY WITH AGING

Recent studies have revealed additional substrates for 11β-HSD1. These include additional functions in the metabolism of neurosteroids such as dehydroepiandrosterone (DHEA) and pregnenolone, metabolism of 7-oxysterols, as well as in the detoxification of various xenobiotics (Odermatt and Nashev, 2010). Neurosteroids have long been implicated to play an important role in the modulation of spatial learning and memory processes (Vallee et al., 2001). Circulating levels of DHEA derive from the adrenal cortex and decline significantly with aging in humans and this parallels cognitive decline (Orentreich et al., 1992). In rodents there is very little DHEA in brain because they lack adrenal expression of the enzyme cyp17α that converts pregnenolone to DHEA (Le Goascogne et al., 1991) though there may be limited

local CNS synthesis (Liu et al., 2009). However, high levels of its precursor pregnenolone have been measured in the hippocampus of young rats and this declines with aging correlating with spatial memory impairments (Vallee et al., 1997). Pregnenolone, DHEA, and related 3β-hydroxysteroids are 7α-hydroxylated in brain by the cytochrome P450-7B1 (CYP7B1) enzyme into their bioactive steroid metabolites (Rose et al., 1997). High levels of CYP7B1 is expressed in the hippocampus and enzyme activity is selectively decreased in aged rats with impaired spatial memory but not in aged cognitively unimpaired rats (Yau et al., 2006). In the memory-impaired aged rats, central administration of an active product, 7α-hydroxypregnenolone, reversed the spatial memory deficits and improved memory in a radial arm watermaze memory task thus effectively overcoming reduced CYP7B1 activity in the aged brain (Yau et al., 2006). It has recently been proposed that the products of CYP7B1, 7α-hydroxypregnenolone, and 7α-hydroxyDHEA, may exert anti-GC effects in target tissues by competing with 11-keto GCs for access to 11β-HSD1, thus attenuating regeneration of active GCs (Muller et al., 2006a). Thus, 11β-HSD1, in addition to its known role in reactivating GCs within target cells, has also been shown to carry out the inter-conversion of 7α-hydroxyDHEA into 7β-hydroxyDHEA, at least *in vitro* (Muller et al., 2006b) (**Figure 5**). Enzyme kinetic data from yeast-expressed human 11β-HSD1 implies that the 7-hydroxysteroid substrates are preferred to cortisone. Hence in tissues, 7-hydroxysteroid substrates may act like endogenous "inhibitors" of 11β-HSD1, reducing their regeneration of active GCs. This adds another level of potential fine tuning of GC action within specific target CNS cells but whether this occurs *in vivo* under normal or pathological conditions is not known.

CONCLUSIONS

The local amplification of GC action in the brain by 11β-HSD1 plays a pivotal role in the emergence of spatial learning impairments with aging. Evidence over the past decade has confirmed that while elevated plasma GCs correlate with impaired spatial learning with aging, it is the level of active GCs within specific brain cells regulated by 11β-HSD1 that appears essential for the control of spatial memory in the aged animal. Importantly, whereas treatments to lower blood GC levels need to be maintained long-term to ameliorate spatial memory deficits in aged rats, lowering GC levels inside cells expressing the enzyme by selective 11β-HSD1 inhibitors requires only short-term treatment and can reverse spatial memory deficits in already aged mice. Whether this is the case in humans remains to be tested. The data also show that spatial memory deficits in aged rodents are not necessarily irreversible due to structural changes but appear to be regulated in the short-term by intracellular GC actions activating MR and GR to regulate the transcription of target genes that influence memory formation. Future investigations to determine

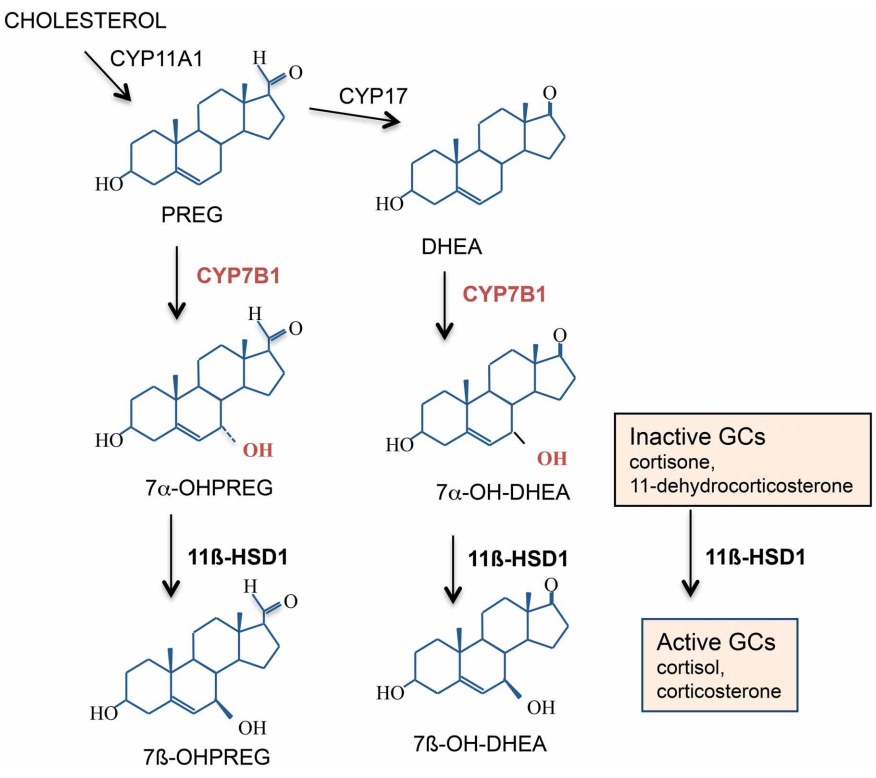

FIGURE 5 | 7α-Hydroxylated steroids are also substrates for 11β-HSD1. Both 11β-HSD1 and CYP7B1 are expressed in the rodent and human hippocampus. CYP7B1 7α-hydroxylates pregnenolone (PREG) and dehydroepiandrosterone (DHEA) into their more active 7α-hydroxylated metabolites which are also substrates for 11β-HSD1. If levels of these 7α-hydroxylated metabolites within specific cells become high enough, they may compete with the inactive GCs for 11β-HSD1 and effectively act as endogenous "inhibitors" of 11β-HSD1 amplification of intracellular GC action.

the mechanisms whereby 11β-HSD1 in the brain is upregulated by aging and the downstream pathways following predominant brain MR activation in aged 11β-HSD1 KO mice will be crucial in the understanding of how GCs maintain or impair hippocampus-dependent spatial learning and memory with aging. Whether or not this approach is of utility in pathological brain aging, such as Alzheimer's disease and other dementias, remains to be determined, but of substantial interest.

ACKNOWLEDGMENTS

The authors' work was supported by project grants from The Wellcome Trust, BBSRC, MRC, and fellowships (Joyce L. W. Yau) from Alzheimer's Research UK and RCUK. The authors are members of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative. Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 25 May 2012; paper pending published: 18 June 2012; accepted: 02 August 2012; published online: 29 August 2012.

Citation: Yau JLW and Seckl JR (2012) Local amplification of glucocorticoids in the aging brain and impaired spatial memory. Front. Ag. Neurosci. ***4****:24. doi: 10.3389/fnagi.2012.00024*

frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 08 August 2012
doi: 10.3389/fnagi.2012.00022

Age-associated changes in the hippocampal-ventral striatum-ventral tegmental loop that impact learning, prediction, and context discrimination

Marsha R. Penner and Sheri J. Y. Mizumori*

Laboratory of Neural Systems, Decision Science, Learning and Memory, Department of Psychology, University of Washington, Seattle, WA, USA

Edited by:
Paul A. Dudchenko, University of Stirling, UK

Reviewed by:
Daniel Ortuño-Sahagun, Centro Universitario de Ciencias Biológicas y Agropecuarias, Mexico
David Bett, University of Edinburgh, UK

****Correspondence:***
Sheri J. Y. Mizumori, Department of Psychology, University of Washington, Box 351525 Guthrie Hall, Seattle, WA 98195, USA.
e-mail: mizumori@uw.edu

Studies of the neural mechanisms of navigation and context discrimination have generated a powerful heuristic for understanding how neural codes, circuits, and computations contribute to accurate behavior as animals traverse and learn about spatially extended environments. It is assumed that memories are updated as a result of spatial experience. The mechanism, however, for such a process is not clear. Here we suggest that one revealing approach to study this issue is to integrate our knowledge about limbic system mediated navigation and context discrimination with knowledge about how midbrain neural circuitry mediates decision-making. This perspective should lead to new and specific neural theories about how choices that we make during navigation determine what information is ultimately learned and remembered. This same circuitry may be involved when past experiences come to bias future spatial perceptions and response selection. With old age come not only important changes in limbic system operations, but also significant decline in the function of midbrain regions that underlie accurate and efficient decisions. Thus, suboptimal accuracy of spatial context-based decision-making may be, at least in part, responsible for the common observation of spatial memory decline in old age.

Keywords: adaptive navigation, context discrimination, decision-making, error prediction, hippocampus, ventral striatum, ventral tegmental area

INTRODUCTION

Cognitive map theory (O'Keefe and Nadel, 1978), which was based on the discovery of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971), suggested that the hippocampus is important for the representation of experiences that occur within a spatial context (Nadel, 2008). These ideas have since been elaborated on, and one current assertion, discussed herein, is that the hippocampus does not just represent context, but also works to discriminate *between* contexts and to determine when a salient feature of a context have changed (Mizumori et al., 1999, 2007a). There is a growing body of experimental evidence providing support for this idea. Moreover, convergent evidence suggests a key role for the hippocampus in age-related impairments of context-based learning and memory. For example, work with rodent, primate, and human subjects shows that a compromised hippocampus results in spatial memory deficits that could be accounted for by poorer analysis of contextual details. These deficits are proposed to have a significant impact on context-dependent decision-making processes.

WHAT IS CONTEXT?

Although there may be some disagreement regarding what features make up or define a context, everyone would probably agree that a context is a multifaceted entity, and that everything we experience takes place within a context. According to Nadel (2008) the features that define a context must be relatively stable, meaning that their relationship to each other remains, even when there is no one there to experience them. Context, as we will use the term in the following discussion, refers to stable background stimuli, such as the geometrical features of a testing room, as well as more abstract features, such as the task demands and internal state that come to help make some aspects of a context more salient than others (see Smith and Mizumori, 2006a).

The detection of changes in context is necessary for both optimal learning and the selection of appropriate behaviors within a given context. In order to determine if a salient feature of a particular context has changed, match–mismatch comparisons are made (**Figure 1**). This allows an organism to determine how similar the current context is to the context the animal was expecting based on past experience (see Mizumori et al., 2007a).

THE HIPPOCAMPUS AND CONTEXT

There is growing evidence that the hippocampus has a special role in learning and memory because it functions to distinguish meaningful contexts, and in that way determine the saliency of different contexts (e.g., Mizumori et al., 1999; Smith and Mizumori, 2006a; Mizumori et al., 2007a; Penner and Mizumori, 2012). This function is critical for the formation of new episodic memories because it separates in time and space one meaningful event from the next. Such "chunking" of memories could facilitate long-term information storage according to memory schemas (Tse et al., 2007; Bethus et al., 2010).

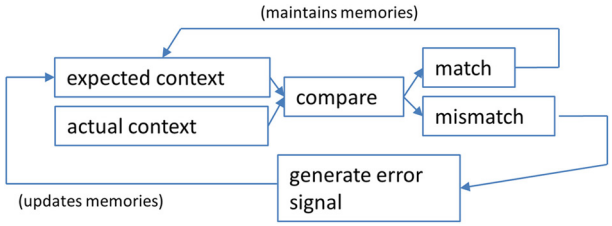

FIGURE 1 | A schematic illustration of the steps involved in a context prediction error analysis. Information about expected features of a given context are compared against actual contextual features experienced by the animal. If they are perceived to be the same, a "match" signal is generated that maintains (or possibly strengthens) the neural network that underlies the current active memory. Pattern completion computations may predominate in such a determination of a match (see text for discussion). If a "mismatch" is detected, the result is hippocampal output that reflects the error in prediction. In this case, pattern separation computations may prevail over pattern completion computations. The impact of a context prediction error signal is to ultimately update long-term memories that will define the expected contextual features the next time an animal enters the same situation.

Studies of the predominant type of neural representation by hippocampal pyramidal neurons, location-selective firing (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978), have provided insight into the mechanisms by which the hippocampus analyzes context information to result in context prediction error signals. As decades of research have shown (summarized in Mizumori et al., 2007a), "place fields" of recorded "place cells" are dynamic and integrated representations of multiple types of information, from sensory, motivational, and behavioral, to mnemonic. 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 re-mapping. Thus, it is the combination of these different types of information that have come to define the meaning of "context" when referring to hippocampal processing. The relative contributions of these different input types vary with task demands, and this is evidenced by findings across many laboratories that place fields change when rats use identical environmental information to solve tasks according to different strategies (e.g., Ferbinteanu and Shapiro, 2003; Kennedy and Shapiro, 2004; Mizumori et al., 2004; Eschenko and Mizumori, 2007). To the extent that different cognitive strategies are mediated by different underlying memories, a particular 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). Thus, when one refers to place field re-mapping, implicit is the notion that each map is driven by a different memory.

Many cleverly designed studies have sought to determine the features and sensory inputs that affect re-mapping of hippocampal place fields. Early studies, for example, showed that place cells are sensitive to changes in the visual environment (e.g., Ranck, 1973; O'Keefe, 1976; Olton et al., 1978; Muller and Kubie, 1987) such as the geometric features of the environment (e.g., Gothard et al., 1996; O'Keefe and Burgess, 1996; Wiener, 1996). Other sensory inputs can also affect place activity, including olfactory cues (Save et al., 2000), auditory cues (O'Keefe and Conway, 1978; McEchron and Disterhoft, 1999), and somatosensory cues (Young et al., 1994). Based on this body of work, it is clear that hippocampal pyramidal neurons process multimodal sensory cue information. 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) tested this idea by training rats to distinguish Context A from Context B according to where reward was expected to be found. Importantly, the motivational, sensory and behavioral requirements of task performance were explicitly held constant across the two contexts so that changes in place fields could be attributed to the recall of a different memory. Place fields were found to reorganize at the beginning of trials in Context B, a time when a match–mismatch comparison may be implemented, and a time when there may be uncertainty about the context. 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.

FROM PREDICTION ERRORS TO CONTEXT DISCRIMINATION: A ROLE FOR THE HIPPOCAMPUS

What kind of computations take place in order for an organism to determine if a salient feature of the context has changed? When an organism's expectations about its experiences are violated, it is adaptive to update expectations so that adequate predictions can be made in the future. Once mismatches between expectations and outcomes no longer occur, learning is considered "complete." According to classic learning theories, learning is driven by errors in the ability to accurately predict the occurrence of rewards, referred to as "prediction errors" (Rescorla and Wagner, 1972; Pearce and Hall, 1980; Sutton, 1988). The most common examples are the Rescorla–Wagner (Rescorla and Wagner, 1972) and temporal difference learning models (Sutton, 1988; Sutton and Barto, 1998) which use errors to drive associative changes. When a large prediction error is generated, a correspondingly large change in associative strength occurs. In contrast, no change in associative strength will occur if the computed prediction error is zero (i.e., the outcome is accurately predicted). Importantly, the relative sign of the error determines whether associative strength is promoted or weakened. When an outcome is better than predicted, the error generated will be positive, resulting in a strengthening of the association between the cues and the outcome. Alternatively, when the outcome is worse than predicted, a negative error signal is generated, and the association will weaken.

The neural instantiation of a reward prediction error was first observed in the midbrain dopamine system (Schultz et al., 1997). Using Pavlovian reward predicting paradigms in monkeys and rodents, it has been shown that dopamine cells increase phasic discharge when new rewards are encountered (Schultz et al., 1997). As the animal learns to expect reward, however, dopamine cell responses to rewards decline (Fiorillo et al., 2003). When this is the case, dopamine cells come to respond not to the reward itself but rather to the cues that predict the reward, such as a tone or light. The finding that reward responses of dopamine cells change from the reward to the cues that predict rewards is mirrored by

corresponding changes in the timing of dopamine release in the nucleus accumbens (Day et al., 2007).

ASSESSING VALUE

The dopaminergic system is also part of a neural network that assesses the value of behavioral outcomes—reward-induced excitation of dopamine neurons scales to the magnitude of rewards (Schultz et al., 1997). Thus, 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 (Schultz et al., 1997) by decreasing their firing rates. The reduction in firing to the absence of expected reward is greater if the expectation was for a large, and not small, reward. A schematic illustration of these different dopamine cell responses to reward can be found in **Figure 2** (left side of figure).

OTHER FUNCTIONS OF DOPAMINE

In addition to generating a reward prediction signal, midbrain dopamine neurons also transmit signals related to salient but non-rewarding experiences such as aversive and alerting events (e.g., Pezze et al., 2001; Pezze and Feldon, 2004; Redgrave and Gurney, 2006). Thus, it has been suggested that dopamine neurons represent a heterogeneous population of cells that are connected to anatomically and functionally distinct brain networks (Bromberg-Martin et al., 2010). This would imply that dopamine neurons can have distinct roles in motivational control; some dopamine neurons may encode motivational value, supporting brain networks for seeking, evaluation, and value learning while others encode motivational salience, supporting brain networks for orienting, cognition, and general motivation (e.g., Berridge, 2007; Smith et al., 2011). For both types of dopamine neurons, an alerting signal could prime these cells for rapid detection of potentially important cues, a computation that would be necessary for detecting salient aspects and/or changes in context (see Bromberg-Martin et al., 2010).

PREDICTION ERRORS IN OTHER BRAIN REGIONS

Neural correlates of reward prediction errors have also been observed outside of the midbrain, in the prefrontal cortex, orbitofrontal cortex, striatum, amygdala, reticular formation, and habenula (Nobre et al., 1999; Schultz and Dickinson, 2000; McClure et al., 2003; Satoh et al., 2003; Bayer and Glimcher, 2005; Fiorillo et al., 2005; Tobler et al., 2006; Yacubian et al., 2006; Belova et al., 2007; Matsumoto and Hikosaka, 2007; Roesch et al., 2007; Puryear and Mizumori, 2008). This suggests that a critical and common function of many brain areas is to provide an outcome expectancy signal or prediction. Evidence is accumulating that the hippocampus is another brain region that may generate error prediction signals.

HIPPOCAMPAL CONTEXT PREDICTION ERROR

It has been suggested that hippocampal neurons represent the contextual features of an environment for the purpose of computing the extent to which familiar contexts change (Nadel and Wilner, 1980; Nadel and Payne, 2002), or more specifically the extent to which expected and actual context features match (e.g., Mizumori et al., 1999; Anderson and Jeffery, 2003; Jeffery et al., 2004; Hasselmo, 2005; Smith and Mizumori, 2006a,b; Nadel, 2008). If the hippocampus determines that there was no change (e.g., a familiar context appears as expected), then the currently active neural network that defines the current memory will be strengthened so that it can continue to drive behavior. If, on the other hand, a mismatch signal is generated, it will alert other neural systems of the brain so that they become prepared for rapid and new learning (**Figure 1**). The mismatch could be considered an example of an error in predicting the contextual details of the current situation and is thus referred to here as a "context prediction error." Transmission of a context prediction error signal can inform distal brain areas that a change in the context has occurred. For example, upon receipt of the hippocampal message, midbrain structures may respond with changes in excitation or inhibition to determine the subjective value of the context prediction error signal. Similarly, the same hippocampal signal may enable plasticity mechanisms (perhaps in neocortex) that 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). In this way, hippocampal context analyses becomes critical for the formation of new episodic memories via a prediction signal that can provide a mechanism that separates in time and space one meaningful event from the next. **Figure 2** shows schematized hippocampal place field responses, based on the vast literature on place field responses to context changes (Mizumori et al., 2007b), that illustrate the relationship between hippocampus and dopamine neurons: when the hippocampus signals a change in context, dopamine cells encode reward value.

HIPPOCAMPAL CHANGES IN THE AGED BRAIN

The natural environment in which we behave continually changes. Optimal learning and performance depends on our ability to detect changes in context with sufficient temporal and informational specificity so that decisions about future adaptive responses can be made. Alterations in the ability of the hippocampus to perform these operations will contribute to significant learning and memory deficits that are manifested by an inability to recognize that something important or salient has changed, as is often observed in aged subjects. There is abundant and consistent evidence from aged rodents, monkeys, and humans that behavioral deficits are often observed on tasks whose optimal solution requires the use of spatial information (Gallagher and Rapp, 1997; Rosenzweig and Barnes, 2003; Wilson et al., 2006). Although neurobiological differences certainly exist across species, the organizational and functional principles governing spatial information processing are strikingly similar from rat to human.

The hippocampal place cells of aged rats show changes that are likely to significantly impact memory and context analysis functions. The initial pioneering work of Barnes (1979) demonstrated significant age-related deficits in spatial memory function that correlated with changes in synaptic plasticity; modification of synaptic efficacy at the perforant path synapses in the dentate gyrus was found to be significantly impaired (Barnes, 1979). Subsequent to this work, Barnes et al. (1983) recorded CA1 place cell activity in adult and aged rats as they performed a forced-choice eight-arm maze task. Rats were not required to

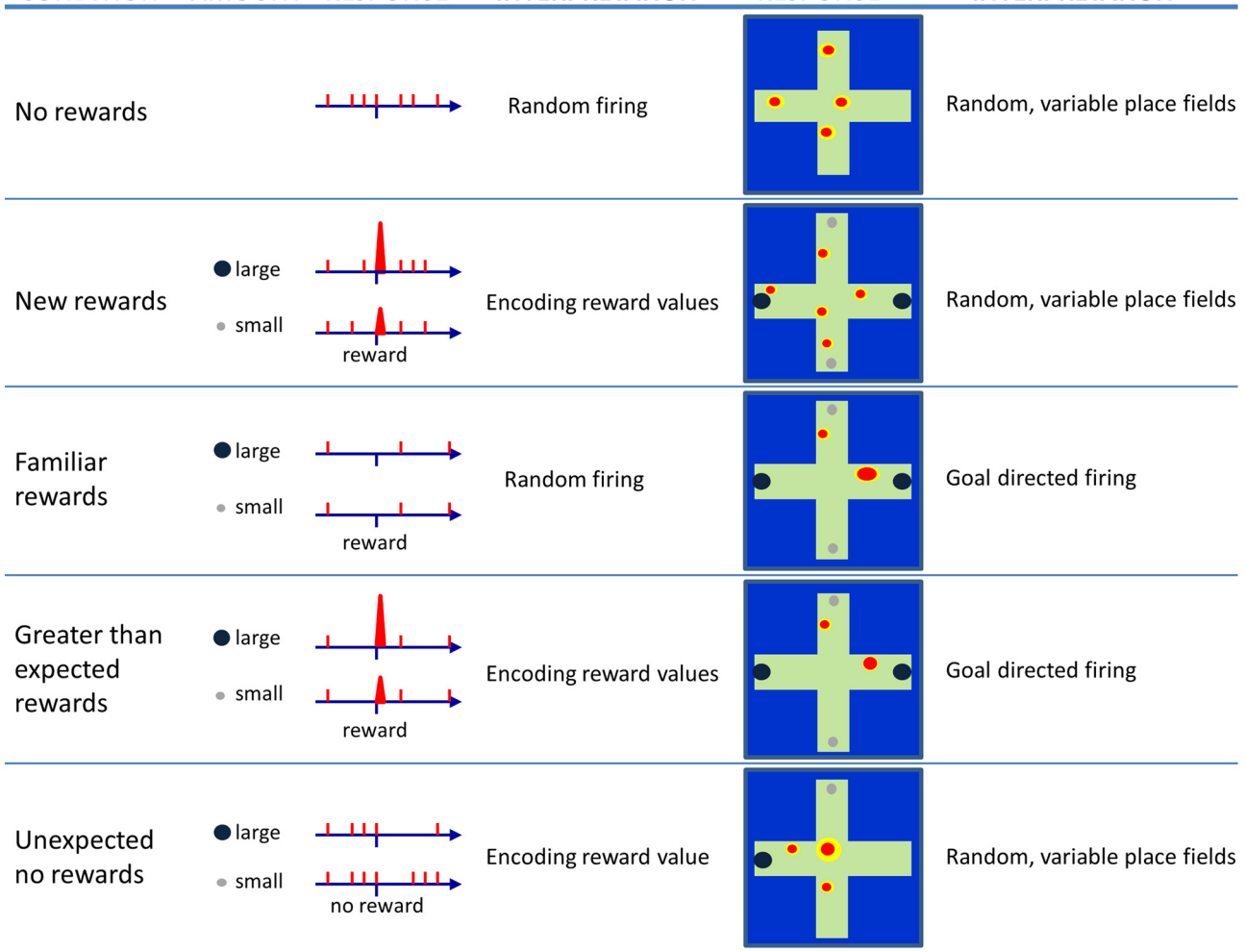

FIGURE 2 | Schematic illustration of dopamine (DA) cell responses to encounters of large or small rewards as a rat solves a maze task under different reward conditions (left). Consistent with the literature, DA cells appear to fire randomly at low rates as animals traverse a maze when no rewards are present (No reward). When a rat encounters reward for the first time (New rewards), DA cells exhibit phasic burst firing to a larger extent following encounters with large rewards than small rewards. In this case, DA cells are considered to be encoding reward values. When the reward-finding task is learned (Familiar rewards), DA cells should no longer fire upon reward encounters. If the rat then unexpectedly encounters reward, one will again observe burst firing by DA cells in proportion to the magnitude of reward (Greater than expected rewards). If a trained rats goes to a location that was previously associated with rewards, but the reward is unexpectedly absent (Unexpected no rewards), then DA cells are observed to show brief periods of inhibited firing that is proportional to the amount of reward expected. The right panels illustrate expected (based on the current literature) place field responses when recorded under the same varying reward conditions. During random activity on a maze, place fields exist but they tend to occur in somewhat random locations. On a trial when new rewards are first encountered, place fields may continue to occur in random locations since the new reward information has yet to update long-term memories. As a task is learned, and locations are associated with specific rewards, one may observe increased place field specificity, and the location of the field may skew toward the rewarded location. If animals encounter larger than expected rewards, the place fields may not change or they may become even more specific to reflect the increased significance of rewarded locations. If on the other hand, a reward is not found at a previously rewarded location, then one may observe place fields to move, or re-map, due to the elevated degree of uncertainty.

remember any spatial information but could access reward arms sequentially. Place fields in aged rats were found to be less place-specific and less reliable, in that they did not fire every time an animal ran through the field. These changes were suggested to contribute to the memory deficits observed in aged rats (Barnes et al., 1983).

Subsequent to this work, Barnes et al. (1997) demonstrated that when aged rats are brought into a familiar environment, they occasionally re-map. That is, there was an occasional global change in the place fields of most or all of the cells being recorded—some fields changed their preferred location within the environment, some cells stop firing in a previously preferred location (i.e., lose a place field), and some previously silent cells began firing (i.e., gained a place field). When this kind of re-mapping occurred during a recording session, the overall place fields appeared "noisy," as was initially demonstrated by Barnes

(Barnes et al., 1983). Importantly, when this re-mapping occurred it did so only when animals re-entered an environment it had previous experience with, never when an animal remained in the environment (Barnes et al., 1997).

Subsequent work, however, reported conflicting results in that the place fields of aged rats were shown to be just as place-specific and stable as those of adult rats, and under some conditions, more so (Markus et al., 1994; Mizumori et al., 1996; Shen et al., 1997; Tanila et al., 1997; Oler and Markus, 2000; Wilson et al., 2003). For example, Tanila et al. (1997) manipulated visual cues within the recording environment, and found that aged, memory-impaired rats were less likely than were adult rats or aged, memory intact rats to re-map in response to major changes in the environment. Thus, instead of being multi-stable, as reported by Barnes et al. (1997), the place cells of aged memory-impaired rats were often impervious to changes in the visual environment.

These results were subsequently reconciled by Wilson et al. (2004) who recorded place cells from aged and young rats as they repeatedly explored either a highly familiar environment or a novel environment. Initially, place cells in aged rats maintained their activity between the familiar and novel environments, suggesting that they were more rigid than those of the younger rats, as had been previously reported by others. However, Wilson et al. (2004) also observed that the rigidity of aged place cells was temporary. With additional experience, new representations of the novel environment could eventually be formed by aged rats, indicating a delay rather than an inability to detect a change in the environment. Finally, once these new spatial representations did develop, they were shown to be multi-stable across repeated exposures to the formerly novel environment. Thus, it appears that significant deficits in the ability of visual cues to control spatial representations of aged rats can manifests in at least three ways: rigidity, delayed control by external cues, and multi-stability (Wilson et al., 2004).

Environments or contexts are composed of more than just visual cues, and these other features can also exert control over place cell firing. Oler and Markus (2000) tested the idea that task demands, rather than spatial cue-based manipulations, would differentially impact changes in place field characteristics in young and aged rats. To test this idea, rats moved through a figure eight maze to retrieve chocolate rewards. The maze configuration was then changed to a plus maze configuration. Importantly, the maze remained in the same testing environment, so visual cues within the testing room remained unchanged. Rats were then required to run the plus maze, and after several laps, the maze was again restored to a figure eight configuration. Recordings from hippocampal place fields changed their spatial firing preference between the two maze configurations in younger rats, but this change did not occur in aged rats. Instead, place cells in the aged hippocampus retained their spatial firing pattern even though the task demands had changed. These results demonstrate that hippocampal place cells in young rats encode task-related information within a relatively stable spatial context while aged rats show deficits in encoding this information. The possibility remains that old rats were simply delayed in encoding changes in task demands, as described by Wilson et al. (2004). This idea has not yet been explicitly tested.

The work discussed thus far pooled data obtained from different subregions of the hippocampus (CA1 and CA3) in order to increase statistical power. It is now appreciated, however, that subareas of the hippocampus perform different information processing tasks and have different place field characteristics. These differences are a direct result of differences in their efferent and afferent projections, and this makes them differentially sensitive to context manipulations that produce re-mapping. For example, the CA3 subregion receives excitatory inputs from the mossy fibers of dentate granule cells, layer II of the entorhinal cortex, as well as a recurrent network of densely interconnected CA3 pyramidal cells, making it particularly suited for rapid learning of environment-specific features (Nakazawa et al., 2003). Work by several groups have shown that CA3 pyramidal cells exhibit an all-or-nothing change in their firing patterns when familiar environments are changed, or new environments are encountered (Lee et al., 2004; Leutgeb et al., 2004; Vazdarjanova and Guzowski, 2004; Miyashita et al., 2009). Conversely, area CA1 receives excitatory input from CA3 via Schaffer collaterals and the entorhinal cortex but has extremely limited intrinsic excitatory connections. When changes to familiar environments are encountered, area CA1 has been shown to display a gradual change in firing patterns. This has led some to suggest that area CA1 acts as a "comparator," in that it determines if a change in context has occurred by comparing the outputs of CA3 with direct inputs from the entorhinal cortex (Mizumori et al., 1999; Leutgeb et al., 2004; Vazdarjanova and Guzowski, 2004).

To test the idea that specific subregions of the hippocampus may be selectively vulnerable to effects of the normal aging processes, Wilson et al. (2004) compared the spatial firing patterns of CA1 and CA3 neurons in aged memory-impaired rats with those of young rats as they explored familiar and novel environments. Within area CA1, place cells in aged and young rats had similar firing characteristics in both familiar and novel environments. In contrast, within area CA3, aged rats showed place cells with higher firing rates when compared to young rats. In addition, CA3 place cells of aged rats failed to change their firing rates and place fields to the same degree that CA3 cells of young rats did when the rats were introduced to a novel environment. Thus, aged CA3 cells failed to rapidly encode new spatial information compared with young CA3 cells, suggesting a unique contribution of CA3 dysfunction to age-related memory impairment and context discrimination. In fact, these results are supported by the finding that a complete ensemble of CA3 pyramidal neurons are activated by a single exposure to a context, whereas CA1 cells require multiple exposures in order for a complete ensemble to be activated (Miyashita et al., 2009).

The dentate gyrus is another subregion of the hippocampus that is likely to contribute to a context discrimination function. Because sparse firing patterns are characteristic of dentate granule cells make it technically challenging to record from these cells, a relative dearth of *in vivo* electrophysiology data has been collected from this brain region. Other methods, including immediate-early gene imaging and fMRI studies have provided extensive evidence that this subarea of the hippocampus is particularly vulnerable to normative aging processes (Small et al., 2004; Penner et al., 2011).

COMPUTATIONAL MECHANISMS THAT SUPPORT CONTEXT DISCRIMINIATION

Detecting a change in context is a necessary computation if one needs to discriminate contexts. Originating in the work of Marr (1971), pattern separation and completion computations are two functions that are widely attributed to specific subregions of the hippocampus (Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; Samsonovich and McNaughton, 1997). Pattern completion is the process through which incomplete, noisy or degraded input are filled in based on representations that have previously been stored. In this way, complete episodes/memories can be recalled without a complete set of inputs. Pattern separation, on the other hand, is a computation that orthogonalizes similar inputs/representations. This functions to make similar inputs as dissimilar as possible, so that similar episodes/memories can be distinguished (Guzowski et al., 2004; Yassa and Stark, 2011). The interplay between these processes determines the extent to which hippocampal output signals a context prediction error: if pattern completion is greater than pattern separation, the hippocampal output signals a "match," whereas conditions in which pattern separation is greater than pattern completion should generate a mismatch (or prediction error) signal (Mizumori, 2008). Specific subareas of the hippocampus may compute the degrees of pattern separation and completion. Both theoretical models and experimental work suggest that the granule cells of the dentate gyrus perform pattern separation functions on the input received from the entorhinal cortex. Area CA3 is envisaged as an auto associative network and is therefore ideal for pattern completion functions on inputs received from the dentate gyrus and its own recurrent collaterals. Because of the unique pattern of excitatory inputs to area CA3, this subarea can also perform a pattern separation function. This function may be supported by a subset of neurons within the entorhinal cortex that bypass the dentate gyrus, and thus provide direct input to area CA3. This weaker input can compete with the input from mossy fibers of the dentate gyrus, and thus area CA3 may be well equipped to perform both pattern completion and pattern separation functions (Guzowski et al., 2004; Yassa and Stark, 2011).

In sum, the result of pattern separation and pattern completion computations determines the extent to which hippocampus generates a context prediction signal that can be broadcast to other brain regions for the purposes of modifying behavior that is appropriate for the current context. The work discussed here suggests that aged rats show impairments in both pattern separation and pattern completion computations, resulting in hippocampal representations of contexts that can be either too rigid, or too plastic. Impaired pattern completion in aged rats might cause the occasional retrieval of an incorrect map (especially for CA3 place fields) upon entry to a familiar environment, while impaired pattern separation in aged rats might prevent the formation of a new map in response to environmental changes (Yassa and Stark, 2011).

As discussed above, studies of place cell firing characteristics between adult and aged rats initially produced conflicting results. In some cases, it appeared that hippocampal cells engaged in too much pattern separation, resulting in multi-stable or unstable place fields, while in other instances, it appeared that the reverse was true (e.g., Barnes et al., 1997; Tanila et al., 1997). These results were subsequently reconciled (Wilson et al., 2004, 2005), especially in the case when recordings from CA3 and CA1 were analyzed separately (Wilson et al., 2005). These processes have since been investigated in human subjects (e.g., Bakker et al., 2008; Lacy et al., 2011), and recent work has shown age-related changes in these processes (Stark et al., 2010; Yassa et al., 2011a,b; Holden et al., 2012). For example, Yassa et al. (2011a) tested the ability of young and aged adults to discriminate between novel, familiar or similar objects and with measuring BOLD activity in the hippocampus during performance of the task. They observed a behavioral impairment in pattern separation for the aged adults compared to the young controls. These findings were related to an increase in CA3/dentate gyrus activity, a finding reminiscent of animal work showing hyperactivity in area CA3 (Wilson et al., 2004). In addition, Yassa et al. (2011a) found that larger changes in the input (greater dissimilarity) were necessary in order for aged adults to successfully encode new information as distinct from previously learned information.

TARGETS OF THE CONTEXT PREDICTION SIGNAL

The hippocampus is hypothesized to provide a context prediction error signal to other areas of the brain in order to determine if expectations about the current context have been met, or if they need to be updated. The hippocampus is directly connected to both the ventral striatum (also known as the nucleus accumbens) and the prefrontal cortex, and these structures are therefore direct recipients of the hippocampal context prediction error. In addition, the hippocampus regulates activity within the ventral tegmental area (VTA) via its effects on the ventral striatum (Yang and Mogenson, 1987; Floresco et al., 2001) and via the lateral septum (Luo et al., 2011). The following discussion will focus on contextual information processing within the hippocampal-ventral striatal-VTA loop (Voorn et al., 2004; Pennartz et al., 2009, 2011; Humphries and Prescott, 2010).

HIPPOCAMPUS-VENTRAL STRIATUM INTERACTIONS

The ventral striatum is often referred to a limbic-motor interface (Mogenson et al., 1980). It receives convergent glutamatergic input from multiple sensory and association areas of the neocortex, and the limbic system, including the hippocampus and related structures (for review see Humphries and Prescott, 2010). The nucleus accumbens, the main structure of the ventral striatum, can be divided into core and shell subregions, which differ significantly in terms of their cellular morphology, neurochemistry, and patterns of projections. The shell receives hippocampal input predominantly from ventral CA1 and subiculum, whereas the core receives it from dorsal CA1 and subiculum and from parahippocampal regions (Voorn et al., 2004).

The ventral striatum is not only important for processing spatial and contextual cues (Annett et al., 1989; Seamans and Phillips, 1994; Floresco et al., 1997; Ferretti et al., 2010), but also processes information relevant to effort and cost-based decision-making (e.g., Aberman et al., 1998; Aberman and Salamone, 1999; Hauber and Sommer, 2009; Day et al., 2011). The ability to make these kinds of decisions is essential if animals are to make adaptive

behavioral choices within a given context. The ventral striatum appears strategically positioned to play a key role in context-dependent value-based decisions given the convergent evidence from a variety of maze studies, including the spatial version of the Morris swim task (Setlow and McGaugh, 1998; Sargolini et al., 2003), the radial maze (Gal et al., 1997; Smith-Roe et al., 1999), a spatial version of the hole board task (Maldonado-Irizarry and Kelley, 1995), as well as a task in which the animals are required to discriminate a spatial displacement of objects (Annett et al., 1989; Seamans and Phillips, 1994; Ferretti et al., 2010).

To investigate the idea that the ventral striatum associates spatial context with reward information, Lavoie and Mizumori (1994) recorded neural activity in the ventral striatum while rats navigated an eight-arm radial maze for food reward. This study demonstrated, for the first time, spatial firing correlates within the ventral striatum. The mean place specificity for all ventral striatal neurons was significantly lower than that typically observed in the hippocampus (Barnes et al., 1990), indicating that while ventral striatal neurons discharge with spatial selectivity, they are not as selective as those observed from hippocampal neurons. The moderate spatial selectivity likely reflects the integration of spatial with other non-spatial information within the ventral striatum, including reward and movement. The fact that single ventral striatal neurons encode multiple types of information supports the view that spatial, reward, and movement information may be integrated at the level of individual ventral striatal neurons (Lavoie and Mizumori, 1994; Pennartz et al., 2011). Recent evidence suggests that spatial information within the ventral striatum is derived from the hippocampus. Ito et al. (2008) showed that an interruption of information sharing between the hippocampus and shell of the nucleus accumbens disrupted the acquisition of context-dependent retrieval of cue information, suggesting that the shell, in particular, may provide a site at which spatial and salient cue information may be integrated.

FROM THE VENTRAL STRIATUM TO MIDBRAIN

Signals originating in the nucleus accumbens impact VTA dopamine neurons via two main routes (**Figure 3**): a direct inhibitory GABAergic synaptic input from the accumbens itself (e.g., Heimer et al., 1991; Kalivas et al., 1993) or an indirect route that includes the ventral pallidum and the pedunculopontine nucleus (PPTg; e.g., Floresco et al., 2003; Zweifel et al., 2009). The direct route may relay information about the expected features of a context while the indirect route may relay information about the actual context features (Humphries and Prescott, 2010; Penner and Mizumori, 2012). Since the direct projection is inhibitory onto dopamine cells, and the indirect route is excitatory, hippocampal signals indicating that a familiar context has not changed (i.e., there is no mismatch of expected and actual context information) would result in equal input from direct (−) and indirect (+) pathways. The result is that dopamine cells should show no change in baseline responding when rewards are encountered. Indeed, under such circumstances dopamine cells do not respond to rewards (e.g., Schultz et al., 1997). In the event that hippocampus signals a change in context (i.e., a mismatch between expected and actual contextual features) the indirect input would be stronger than the direct input. The resultant increased excitability after input from the indirect pathway could make more likely a dopamine cell response to a subsequent reward encountered. Indeed dopamine cells are known to increase responding to rewards after a context change (e.g., Schultz et al., 1997; Puryear et al., 2010). Thus dopamine neurons may be placed on high alert after a change in context is detected, and in that way be better prepared to determine the subjective value of the hippocampal prediction error signal.

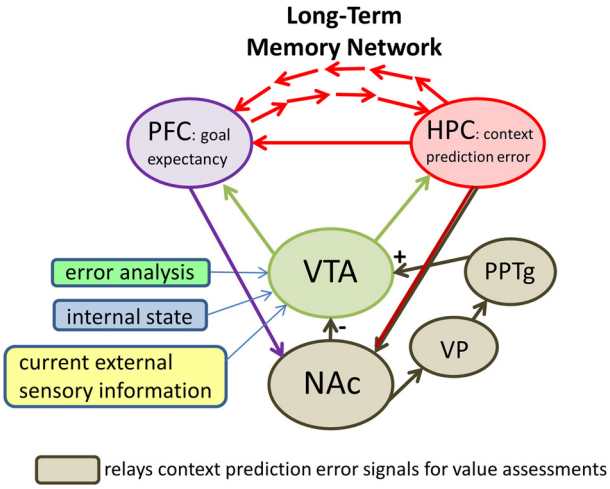

FIGURE 3 | A proposed neural circuit illustrating that midbrain (dopamine) systems and the prefrontal cortex (PFC) are key brain areas that evaluate the significance of hippocampal (HPC) context prediction error signals for the purpose of directing future behaviors and updating long-term memories. Direct HPC output arrives in the midbrain system via projections to the ventral striatum (i.e., the nucleus accumbens, or NAc). The NAc determines whether the outcomes of behavior are as predicted based on an animal's expectations for a given context. If the outcome is as expected, NAc continues exerting inhibitory control (−) over ventral tegmental area (VTA) neurons. In this case, encounters with rewards do not result in dopamine cell firing. In constrast, context prediction error signals from the HPC to the NAc may preferentially excite (+) VTA neurons via an indirect pathway that includes the ventral pallidum (VP) and the pedunculopontine nucleus (PPTg). The result of this elevated excitation may be a depolarization of VTA neurons such that they are more likely to fire when subsequent reward information arrives in VTA. Also influencing the likelihood that dopamine cells will fire in response to future rewards are specific computations that reflect negative reward prediction errors (reward prediction error analysis), information about the animal's current motivational and behavioral state (internal state), and additional information about the current salient cues (current external sensory information). The latter appears to involve at least the PPTg. The impact of the prefrontal cortex on VTA function is not clear. One possibility is that it provides the midbrain circuitry with information about what to expect in terms of goals based on past experience. The summed input to the VTA results in an output that reflects the subjective value of context prediction error signals.

AGING OF THE VENTRAL STRIATUM

There is a limited literature investigating the effects that the normal aging process has on function of the ventral striatum. Much of what is known has come from human work. For example, Schott et al. (2007) used fMRI to investigate the neural mechanisms underlying reward prediction and reward outcome

processing in young and elderly healthy subjects. Young adults showed a pattern of midbrain and ventral striatal activation for cues that predicted monetary reward when compared with cues that predicted neutral feedback. In contrast, healthy aged subjects showed the opposite pattern: an absent reward prediction response in the face of mesolimbic activation to reward feedback itself. This may reflect a reduced ability of older subjects to accurately estimate expected rewards. These results support other behavioral results indicating that older adults have deficits in learning from positive feedback (e.g., Mell et al., 2005).

HIPPOCAMPAL-VTA INTERACTIONS

The VTA and hippocampus reciprocally interact such that novel, context information detected by the hippocampus enhances VTA dopamine release. This in turn enables encoding of new information into long-term memory (Lisman and Grace, 2005; Bethus et al., 2010). Input from the VTA to the hippocampus is direct (Gasbarri et al., 1994), whereas hippocampal output to VTA is indirect, arriving via the lateral septum (Luo et al., 2011) and the ventral striatum (Yang and Mogenson, 1987; Floresco et al., 2001). As evidence of the functional significance of VTA-hippocampus interactions, the VTA has been shown to regulate hippocampal activity and spatial learning (Martig et al., 2009; Martig and Mizumori, 2011a,b) and encoding of hippocampus-dependent memories (Rossato et al., 2009). In addition, the hippocampus has been shown to regulate dopamine responses to novelty (Legault and Wise, 2001) and analogous to hippocampal place fields, phasic reward responses of putative dopamine neurons in VTA are sensitive to changes in the visuo-spatial context (Puryear et al., 2010).

Recent work by Luo et al. (2011) has identified a circuit from area CA3 of the dorsal hippocampus to the VTA that uses the lateral septum as a relay. When area CA3 is stimulated, dopaminergic neurons within the VTA are excited, while non-DA neurons are inhibited. The observed excitation of dopamine neurons is likely mediated by disinhibition because local antagonism of GABA receptors can block the response to CA3 stimulation. Conversely, inactivating components of this circuit blocked evoked responses in VTA and also had a significant impact on reinstatement of drug-seeking by contextual stimuli. Thus, the link between the hippocampus and the VTA may be an important substrate by which information about the environmental context regulates goal-directed behavior. Efficient reward-seeking requires that environmental stimuli be interpreted, allowing accurate predictions about when and where reward can be expected. It is possible that dorsal CA3 conveys information to VTA about the current context as a whole, which allows rapid activation of dopamine neurons to promote salience attribution to conditioned contexts. Such processing is important for cognitive function by providing adjustments in behavior in response to changing real-world environments.

AGING OF THE DOPAMINE SYSTEM

A number of age-related changes in the dopamine system have been demonstrated (for review, see Backman et al., 2006, 2010). Most of this work has been done in non-human primate and human subjects and have for the most part focused on changes that occur in the striatal and frontal cortical areas of the brain. For example, dopamine concentration (Goldman-Rakic and Brown, 1981), transporter availability and binding potential (e.g., Volkow et al., 1998a,b; Mozley et al., 2001), and dopamine D1 and D2 receptor density (e.g., Volkow et al., 1996; Wang et al., 1998; Backman et al., 2000) all decline with age. In addition, work by Kaasinen et al. (2000) found significant age-related declines of D2/3 receptors in all brain regions studied, including the frontal cortical areas, and the hippocampus (Kaasinen et al., 2000). Importantly, for all of the studies mentioned here, these changes occur in the absence of pathological aging, such as Parkinson's and Alzheimer's disease. Treatment of aged monkeys with a D2 receptor agonist reduces the decline in performance on a delayed memory task (Arnsten and Goldman-Rakic, 1985). In addition, imaging of D2 receptors in humans has found a correlation between receptor availability and performance on attention and response inhibition tasks and on the Wisconsin Card Sorting Task, and have also shown that striatal D2 receptor binding accounts for a greater amount of variation in performance on processing speed and episodic memory tasks than does chronological age (Volkow et al., 1998a; Backman et al., 2000). Based on these findings, it has been proposed that age-related deficits in learning are the result of a decline in dopaminergic function in older age (Nieuwenhuis et al., 2002; Backman et al., 2006, 2010). To date, data on the effects that the normal aging process may have on the midbrain, especially the VTA itself are sparse. However, there is some evidence indicating that significant age-associated changes in dopamine transporter activity within the VTA (e.g., Cruz-Muros et al., 2009).

THE IMPACT OF AGING ON CONTEXT-DEPENDENT DECISION-MAKING BEHAVIORS

Decision-making is the process of choosing an option or course of action from among a set of alternatives. This process depends on the decision-maker's estimate of the outcome of the different options (Rangel et al., 2008). Because memory has a significant impact on the ability of an organism to make the "best" decision in a given context, it may not be surprising that aging affects decision-making behaviors. Determining the subjective value of behavioral outcomes requires an assessment of the extent to which expected rewards are actually received. While it is true that a number of factors are likely to contribute to the definition of one's expectations for behavioral outcomes, the most obvious factor is whether there is an expectation based on past experience. Presumably if there is no history of obtaining rewards in a particular context, then there should be no expectation for a reward. If, however, there is some kind of expectation of reward because of past experiences, then the degree of expectation (i.e., subjective goal values) can be enhanced or reduced (Schultz et al., 2008). The ability to learn from feedback and adaptively change behavior according to positive and negative outcomes is significantly impaired in aged subjects (Samanez-Larkin et al., 2007; Zamarian et al., 2008; Eppinger et al., 2010, 2011; Herbert et al., 2011). In addition, older adults are impaired at learning if reward delivery is probabilistic, a time when predicted outcomes are unreliable. When, however, reward contingencies are deterministic (certain) older adults are able to learn as well as young adults.

Older adults' learning impairments under reward uncertainty may reflect deficits in the ability to form and update value (outcome) representations using prediction error signals. Since learning and the formation of new memories is driven by the ability to respond to prediction error signals, it would be expected that individuals (e.g., aged adults) who suffer from responding appropriately to error signals would also show impaired learning and memory.

Assessments of subjective goal values, then, may change when hippocampus generates context error signals. The ultimate dopamine cell response to such hippocampal input reflects a subjective value that can be ascribed to the context change. How subjective value is computed is not understood. One factor that is sure to come into play is efficient learning strategies within a given context. For example, if an aged organism is unable to learn about the reward contingencies within a given environment, perhaps because of insufficient or erroneous prediction codes, then adaptive choices within a given context will be impaired. It appears that regulation of the dopamine cell phasic firing by hippocampus may control the "teaching" signal that is often attributed to dopamine neurons (e.g., Luo et al., 2011), a signal that informs neural circuitry that makes decisions about the selection of future responses.

SUMMARY AND SUGGESTIONS FOR FUTURE WORK

The work presented here highlights a fundamental role for the hippocampus in context discrimination. While the hippocampus may be especially important for detecting and responding to the spatial features of context, it is becoming increasingly clear that the hippocampus is also sensitive to non-spatial aspects of a context, including other sensory cues, task demands, and internal factors such as hunger or thirst. When salient aspects of a context change, the hippocampus is in a unique position to broadcast a teaching signal in the form of a context prediction error signal to other brain areas to which it is closely connected, including the ventral striatum and VTA. These brain regions then assist the hippocampus in determining if salient features of a context have, in fact, changed. Functional changes in the hippocampus that occur during the normal aging process result in significant deficits in the ability to accurately determine if a change in context has occurred. For example, an age-related deficit in the ability to discriminate contexts by the hippocampus will result in inefficient signals that would normally prepare other connected brains regions (e.g., the midbrain, ventral striatum, and prefrontal cortex) for the plasticity required to adaptively respond. Although not discussed here, additional brain regions are likely to contribute to the learning and memory deficits observed in aged subjects. For example, the prefrontal cortex, dorsal striatum, and amygdala are likely to contribute to context discrimination processes under certain conditions.

Dopamine signaling within the VTA has a significant impact on the ability of both the ventral striatum and the hippocampus to integrate reward and spatial information. Changes in dopaminergic signaling, then, are also important for determining if salient changes in context have occurred. Although not discussed, there is experimental evidence that other neuromodulatory systems, including acetylcholine and serotonin are affected by normative aging processes (see Wilson et al., 2006; Eppinger et al., 2011) and may contribute to a failure to accurately detect contextual changes. In addition, although it is clear that many changes in dopamine signaling occur, evidence remains relatively sparse in terms of how age affects information processing within the VTA itself. Thus, this is a particular area of research ripe for further investigation.

ACKNOWLEDGMENTS

We thank Dr. Van Redila, Valerie Tryon and Jack Clearman for helpful comments on a previous version. This work is funded by NIMH grant MH58755.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 May 2012; paper pending published: 01 June 2012; accepted: 23 July 2012; published online: 08 August 2012.

*Citation: Penner MR and Mizumori SJY (2012) Age-associated changes in the hippocampal-ventral striatum-ventral tegmental loop that impact learning, prediction, and context discrimination. Front. Ag. Neurosci. **4**:22. doi: 10.3389/fnagi.2012.00022*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 04 July 2012
doi: 10.3389/fnagi.2012.00017

The relationship of topographical memory performance to regional neurodegeneration in Alzheimer's disease

George Pengas[1†], Guy B. Williams[1], Julio Acosta-Cabronero[1], Tom W. J. Ash[1†], Young T. Hong[1], David Izquierdo-Garcia[1†], Tim D. Fryer[1], John R. Hodges[2] and Peter J. Nestor[1]*

[1] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[2] Neuroscience Research Australia, Sydney, NSW, Australia

Edited by:
Thomas Wolbers, University of Edinburgh, UK

Reviewed by:
Junming Wang, University of Mississippi Medical Center, USA
J. Arturo García-Horsman, University of Helsinki, Finland
Stefan Klöppel, University of Freiburg, Germany

***Correspondence:**
Peter J. Nestor, Department of Clinical Neurosciences, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences, Robinson Way, CB2 0SZ, Cambridge, UK.
e-mail: pjn23@hermes.cam.ac.uk

†Present address:
George Pengas, Department of Neurology, Portsmouth University Hospitals NHS Trust, Portsmouth, UK.
Tom W. J. Ash, The Technology Partnership plc, Melbourn, UK.
David Izquierdo-Garcia, Mount Sinai School of Medicine, Translational and Molecular Imaging Institute, New York, NY, USA.

The network activated during normal route learning shares considerable homology with the network of degeneration in the earliest symptomatic stages of Alzheimer's disease (AD). This inspired the virtual route learning test (VRLT) in which patients learn routes in a virtual reality environment. This study investigated the neural basis of VRLT performance in AD to test whether impairment was underpinned by a network or by the widely held explanation of hippocampal degeneration. VRLT score in a mild AD cohort was regressed against gray matter (GM) density and diffusion tensor metrics of white matter (WM) ($n = 30$), and, cerebral glucose metabolism ($n = 26$), using a mass univariate approach. GM density and cerebral metabolism were then submitted to a multivariate analysis [support vector regression (SVR)] to examine whether there was a network associated with task performance. Univariate analyses of GM density, metabolism and WM axial diffusion converged on the vicinity of the retrosplenial/posterior cingulate cortex, isthmus and, possibly, hippocampal tail. The multivariate analysis revealed a significant, right hemisphere-predominant, network level correlation with cerebral metabolism; this comprised areas common to both activation in normal route learning and early degeneration in AD (retrosplenial and lateral parietal cortices). It also identified right medio-dorsal thalamus (part of the limbic-diencephalic hypometabolic network of early AD) and right caudate nucleus (activated during normal route learning). These results offer strong evidence that topographical memory impairment in AD relates to damage across a network, in turn offering complimentary lesion evidence to previous studies in healthy volunteers for the neural basis of topographical memory. The results also emphasize that structures beyond the mesial temporal lobe (MTL) contribute to memory impairment in AD—it is too simplistic to view memory impairment in AD as a synonym for hippocampal degeneration.

Keywords: topographical memory, Alzheimer's, MRI, PET, multivariate, support vector, retrosplenial cortex

INTRODUCTION

Memory impairment in Alzheimer's disease (AD) is often assumed to be a consequence of mesial temporal lobe (MTL) degeneration. The reasons for this are self-evident: neurofibrillary tangle (NFT) pathology in AD begins in the MTL (Braak and Braak, 1991); NFT load correlates with cognition in AD (Giannakopoulos et al., 2003); and the hippocampus is known to be atrophic in AD (Jack et al., 1997), including those at the mild cognitive impairment (MCI) stage whose deficit is restricted to memory (Pengas et al., 2010a). Such reasoning, however, might be an oversimplification. For instance, Braak and Braak (1991) used NFTs for their proposed staging protocol, precisely because they observed that NFT pathology followed a progressive pattern in AD; it is therefore expected that NFTs will correlate with other measures of disease severity. Furthermore, it is now well documented that prodromal AD is not simply a "hippocampal" disease: at a presymptomatic stage, carriers of familial, autosomal dominant AD mutations had both accelerated hippocampal and posterior cingulate volume loss (Scahill et al., 2002). This is also true of the MCI-stage of sporadic AD in which there is comparable atrophy of retrosplenial cortex, posterior cingulate cortex and hippocampus (Choo et al., 2010; Pengas et al., 2010a). Indeed, the earliest hypometabolic region identified in AD is the posterior cingulate/retrosplenial cortex (Minoshima et al., 1997; Nestor et al., 2003a) with posterior temporoparietal hypometabolism emerging as the next most affected isocortical region with disease progression (Nestor et al., 2003b; Chetelat et al., 2005).

This constellation of affected regions (MTL, posterior cingulate, retrosplenial cortex, posterior parietal lobe) is homologous with the network activated when healthy volunteers navigate in functional magnetic resonance imaging (MRI) paradigms (Ghaem et al., 1997; Maguire et al., 1998; Burgess et al., 2001; Ino et al., 2002; Shelton and Gabrieli, 2002; Rosenbaum et al., 2004; Wolbers et al., 2004; Wolbers and Buchel, 2005;

Ekstrom and Bookheimer, 2007; Iaria et al., 2007; Ino et al., 2007). It was therefore, previously, hypothesized that topographical memory impairment would be sensitive and specific for early AD. The virtual route learning test (VRLT), in which subjects have to learn routes in a virtual reality environment, was devised and found to be highly sensitive and specific in distinguishing patients with early AD from controls. Moreover, when compared to a range of other memory tests, the VRLT most strongly correlated with real world navigation problems (Pengas et al., 2010b).

To our knowledge, only one previous study has investigated the neural basis of route learning impairment in AD but it did so as a two population voxel-based morphometry (VBM) contrast of gray matter density (GM) in subjects who got lost ($n = 6$ AD plus $n = 5$ MCI) versus those that did not ($n = 4$ AD plus $n = 7$ MCI plus $n = 19$ controls) who did not (deIpolyi et al., 2007). It reported no significant regions in a whole brain analysis but focusing on regions of interest in inferior parietal lobule, parahippocampal gyri and hippocampi, the authors reported atrophy in inferior parietal regions with a rightward bias as well as a tiny area in the right hippocampal tail. The use of regions of interest, the two population design, and inclusion of controls mean that only limited conclusions can be drawn from this study.

The aim of the present study, therefore, was to map the neural substrate for impaired route learning in an unbiased manner with multimodal imaging, using scores from the VRLT, in a cohort of mild AD patients. These behavioral data were derived from the earlier neuropsychological study (Pengas et al., 2010b) and, because the aim of the present work was to understand the basis of route learning impairment in AD, only patients with this condition (i.e., no controls) were included. VRLT scores were regressed with GM density (as a measure of regional brain atrophy), normalized ^{18}F-fluorodeoxyglucose (FDG) radioactivity concentration—used as a measure of resting cerebral glucose metabolism corrected for inter-subject variation in basal metabolism—and diffusion tensor imaging (DTI) parameters of white matter tracts (WM). GM density and FDG data were also examined using a multivariate approach to specifically look at overall network contributions to navigation performance.

METHODS

SUBJECTS

A cohort of $n = 30$ patients with mild AD was identified for the study that had undergone detailed clinical and neuropsychological assessments of whom $n = 16$ patients had MCI (Petersen et al., 2001), and $n = 14$ met National Institute of Neurological and Communicable Diseases and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984) at the time of scanning. The MCI subjects were followed up longitudinally after scanning to confirm progressive decline in all subjects, therefore indicating that their MCI status was due to probable AD. All 30 underwent the MRI protocol and a subset ($n = 26$ of which 14 were designated MCI and 12 AD when scanned) also had FDG—positron emission tomography (PET) imaging (demographics summarized in **Table 1**). These patients were derived from the earlier neuropsychological study of topographical memory in AD (Pengas et al., 2010b). The study was approved by the Local Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee, UK. Written informed consent was obtained from all subjects and care-givers.

Table 1 | Demographics of the AD subjects that were included in the analyses (note: the PET subjects represent a subgroup of the MRI subjects; MMSE: Mini-mental state examination; ACE-r: Addenbrooke's Cognitive Examination-revised).

	MRI subjects Mean ± SD (range)	PET subjects Mean ± SD (range)
N (sex)	30 (17*M*:13*F*)	26 (15*M*:11)
Age, yrs	69.2 ± 5.4 (59–78)	68.8 ± 5.6 (59–78)
Education, yrs	13.8 ± 3.0 (10–19)	13.8 ± 3.1 (10–19)
MMSE	24.6 ± 2.6 (18–28)	24.5 ± 2.6 (18–28)
ACE-r	74.2 ± 10.5 (55–88)	74.3 ± 10.2 (55–88)
VRLT error score	14.5 ± 5.3 (3–23)	14.5 ± 5.1 (3–23)

TOPOGRAPHICAL MEMORY ASSESSMENT

Full details of the VRLT have been previously published (Pengas et al., 2010b). Briefly, the VRLT is s graded route learning task that employs four consecutively harder routes that subjects need to learn and reproduce by navigating with a joystick in a 3D first-person computer-generated virtual town. The task is scored in the number of errors a subject makes to complete all four routes, in a "learning-to-criterion" paradigm (Pengas et al., 2010b).

IMAGING

Image acquisition

MRI. Within days of the behavioral data collection, MR images were acquired on a Siemens Trio 3T system (Siemens Medical Systems, Erlangen, Germany) equipped with gradient coils capable of 45 mT/m and a slew rate of 200T/m/s, and a 12-channel phased-array total imaging matrix head-coil (Siemens Medical Systems, Erlangen, Germany). At acquisition, the field of view was aligned to stereotactic space: the anterior commissure—posterior commissure line was aligned with the axial plane and the inter-hemispheric fissure was aligned along the sagittal plane. In addition, the scanning bed was adjusted to place the scanner isocentre at the thalamus in the mid-sagittal plane. Volumetric T1-weighted images were obtained using 3D magnetisation-prepared radio-frequency pulses and rapid gradient-echo (MP-RAGE) sampling (relaxation time (TR)/ echo time (TE)/ inversion time (TI)/ number of excitations (NEX) = 2300 ms/ 2.86 ms/ 900 ms/ 1; flip angle 9; matrix 192 × 192; 144 slices; voxel size 1.25 × 1.25 × 1.25 mm^3 isotropic). Diffusion-weighted images (DWI) were acquired using a twice-refocused single-shot echo-planar imaging pulse sequence (Reese et al., 2003), with parameters TR/TE/NEX = 7800 ms/ 90 ms/ 1; matrix 96 × 96; 63 contiguous axial slices; isotropic voxel resolution of 2 × 2 × 2 mm^3; bandwidth of 1628 Hz/pixel and echo spacing of 0.72 ms). The diffusion tensor was acquired with diffusion-sensitising gradient orientations along 63 non-collinear directions ($b = 1000$ s/mm^2) that were maximally spread by considering the minimal energy arrangement of point charges on a sphere and one scan without diffusion weighting ($b = 0$ s/mm^2, b0). Parallel acquisition of

independently reconstructed images was allowed for, using generalised autocalibrating partially parallel acquisitions or GRAPPA (Griswold et al., 2002), with acceleration factor of 2 and 39 reference lines.

FDG-PET. FDG-PET scans were acquired within a few weeks of the MRI scans for all patients, using a GE Advance scanner (GE Medical Systems, Milwaukee, WI, USA) in 3D mode (voxel size $2.34 \times 2.34 \times 4.25\,mm^3$, field of view $30.0 \times 30.0 \times 15.3\,cm^3$). Subjects were scanned after a 6 h fast in a dimly lit, quiet room, without using ear-plugs or blindfolds. A 150MBq FDG intravenous bolus injection was given over 30 s. Prior to the acquisition of emission images 35–55 min after injection (4×5 min), a 10 min geometrically windowed, coincidence mode transmission scan was performed using rotating germanium-68 rods for attenuation correction. PET emission images were reconstructed using the PROMIS 3D filtered back-projection algorithm (Kinnahan and Rogers, 1989) with corrections applied for dead time, randoms, normalisation, scatter, attenuation, sensitivity, and decay. Arterial sampling was not performed.

Data processing

Voxel-based morphometry. Statistical parametric mapping 2005 (SPM5, http://fil.ion.ac.uk/spm) was employed to evaluate voxel-wise GM density using VBM (Ashburner and Friston, 2000). Recent studies have shown that skull-stripping and radio-frequency bias correcting MR images improve the performance of warping procedure so this was undertaken using a previously described algorithm (Acosta-Cabronero et al., 2008; Pereira et al., 2010). The resulting warped GM segments were modulated to compensate for volumetric differences introduced into the warped images, and smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. Pre-processing and warping procedures need reasonable initial estimates; hence the origin of each structural volume was set manually to the anterior commissure prior to pre-processing. A relative masking threshold of 0.2 was applied for SPM5 analyses. The GM, WM and cerebrospinal fluid segments from SPM5 were summed together to calculate the total intracranial volume (Pengas et al., 2009), and entered as a nuisance covariate in the statistical regressions.

FDG-PET. Mean FDG (35–55 min) radioactivity concentration maps were generated and their origins were also reset to the anterior commissure. The resulting volumes were skull-stripped using BET2 ($f = 0.7$, $g = 0$) (Smith, 2002), rigidly aligned to their corresponding pre-processed structural image and re-sliced (sinc interpolated) to the voxel size of the structural image using the VTK CISG registration toolkit v2.0.0 (Rueckert et al., 1999). Aligned mean FDG maps were then transformed into stereotactic space using the SPM5 warp transforms of pre-processed volumes and re-sampled to 2 mm isotropic using 7th degree b-spline interpolation. Finally, mean FDG maps were normalized by multiplying all voxels by the scaling factor required to equalize the mean cerebellar radioactivity concentration of each subject to the mean cerebellar radioactivity concentration of all subjects (Ichimiya et al., 1994), and smoothed with a 16 mm FWHM kernel. A relative masking threshold of 0.8 was applied for SPM5 analyses.

Diffusion tensor imaging. The FSL package (http://www.fmrib.ox.ac.uk/fsl/) was employed to process and analyze the DWI data. First, each diffusion-weighted volume was affine-aligned to its corresponding b0 image using FMRIB's linear image registration tool v5.4.2 (Jenkinson and Smith, 2001) to correct for possible motion artefacts and eddy-current distortions. Prior to fitting the tensor, brain masks of each b0 image were generated using BET2 with $f = 0.1$ and $g = 0$. FMRIB's diffusion toolbox v2.0 was then used to fit the tensor and compute the orthogonal elements at each brain voxel, from which fractional anisotropy (FA), axial diffusivity (λ_1), radial diffusivity (RD) and mean diffusivity (MD) metrics were derived. Spatial normalization was performed to a target image; this was the map that required the least amount of non-linear warping to match all other images, which was then affine-aligned into MNI152 standard space. The combination of the two transformations was applied to each subject's FA image, and all warped FA maps were then averaged to create the mean FA template, from which the mean FA skeleton is derived (FA > 0.2). Finally, all subjects' normalized FA, λ_1, RD, and MD data were projected onto the skeleton for statistical analysis. The tract-based spatial statistics (TBSS) approach (Smith et al., 2006), whereby the nearest most relevant tract center in each subject's spatially normalized FA image is projected onto the mean FA skeleton containing the center of all tracts common to all subjects, was used to perform voxel-wise statistics at the tract centers only, thus minimizing the effect of residual misregistration.

Statistical analysis

Univariate analyses. Whole brain analyses were carried out by regressing the VRLT error score with each of the three different imaging modalities: GM density, normalized FDG radioactivity concentration and diffusion metrics (λ_1, RD, MD, and FA). GM density and normalized FDG radioactivity concentration were analyzed using voxel-based multiple linear regressions in SPM5 and illustrated at a statistical threshold of p (uncorrected) < 0.005 and with no voxel extent threshold ($k = 0$). Diffusion analyses employed permutation-based non-parametric inference on unsmoothed statistical maps in TBSS; 10,000 permutations of the data were generated to test against using "randomise v2.1," and cluster-like structures were enhanced using the threshold-free cluster enhancement algorithm (Smith and Nichols, 2009). Previous work has shown that λ_1, MD, and RD can be more sensitive to diffusivity changes in AD than FA (Acosta-Cabronero et al., 2010). Therefore λ_1, MD, RD (in addition to FA) were each assessed using multiple linear regression at p (uncorrected) <0.05. It should be highlighted, however, that there is presently uncertainty as to how changes in these various diffusion metrics relate to neuronal loss in WM; as such, the diffusion analyses should only be considered as exploratory at this time (See "Discussion" also).

Multivariate analyses. Support vector machines for use in regression contexts [support vector regression (SVR)], allow for cognitive scores to be predicted using independently acquired

data such as imaging, and therefore to interrogate the algorithm as to which brain areas influenced the algorithm the most, i.e., which are most relevant to the predicted cognitive score.

The general method of use for statistical learning tools has two phases. The first is a "supervised learning" phase, where the model is "trained" on a subset of the data and is optimized over a cost function, such that it outputs optimal results for that training set. A separate test on the remaining subset of the data then validates the generalizability of the learned model. As the present dataset was relatively small, the data cannot reasonably be split into learning and testing subsets (as small subsets inevitably lead to overfitting), and so cross-validation utilized "leave-one-out" tests instead. In this strategy, one subject's image is removed and the algorithm learns over the rest of the dataset. Then a prediction is made, based on the learned model, for the left-out image. This is then repeated over all subjects, and the accuracy is computed over all tests. The correlation between predicted scores and actual scores for each image then gives a measure of how well the technique performed, and how reliable the model it outputs is. Importantly, if this correlation was not statistically significant, further analyses (to identify relevant brain regions) were not performed.

In the case of regression, optimization takes place by ensuring that predictions over the training set have minimal error, whilst maintaining as robust a predictive function as possible. There are two adjustable parameters, C, the regularisation parameter, which restricts how much influence a single training example can have on the learned model, and ε, an upper bound for the maximum acceptable error allowed without penalty. The predictive form is:

$$Prediction = \sum_{i}^{SVs} \alpha_i k(\boldsymbol{x}_i, \boldsymbol{z}) + b$$

where summation is over all training examples, α's are hyperparameters giving the influence each training example has on the final model, b is a normalisation constant, and $k(\boldsymbol{x}_i, \boldsymbol{z})$ is a kernel function, which allows a model to take a non-linear form.

Visualization of the model is simple in the case of a linear kernel. The functional form of the classifier can be simplified by using the concept of the weight vector, $\boldsymbol{w}$:

$$\boldsymbol{w} = \sum_{i}^{SVs} \alpha_i \boldsymbol{x}_i$$

The predictive form of the SVR technique is then:

$$Prediction = \boldsymbol{w} \cdot \boldsymbol{z} + b$$

As the dot product of weight vector $\boldsymbol{w}$ with test vector $\boldsymbol{z}$ is taken, larger values of $\boldsymbol{w}$ represent regions of the trained model that are more sensitive to change in voxel intensity. In the present study, the SVR was implemented using SVM_light and employing default values from this algorithm for C and ε (Joachims, 1999). Displays of a thresholded version of the weight vector have been previously used in neuroscience work with support vector machines, e.g., Klöppel et al. (2008).

Interpretation of a weight vector is slightly different to interpretation of the more traditional mass univariate scheme. In a mass univariate scheme, an individual voxel is regressed to the score variable, and hence has an individual p-value associated with its correlation. In this multivariate case, a weighted version of the entire field of voxels is regressed to the score variable, and hence it is the overall pattern which has a p-value for correlation—the present technique cannot provide p-values for individual voxels, only for the entire pattern. Given that cognitive functions rely on distributed neural systems, this multivariate methodology is potentially very powerful as it offers the possibility to explain task performance at a network level.

RESULTS

UNIVARIATE ANALYSES

Atrophy (GM density) correlations

VRLT performance correlated bilaterally with GM density in the region of the isthmus/retrospenial junction and extreme tail of the hippocampus. Patchy correlations were also evident in parahippocampal gyrus (PHG), insula, parietal and frontal cortices that were bilateral but with greater right hemisphere involvement (**Figure 1**).

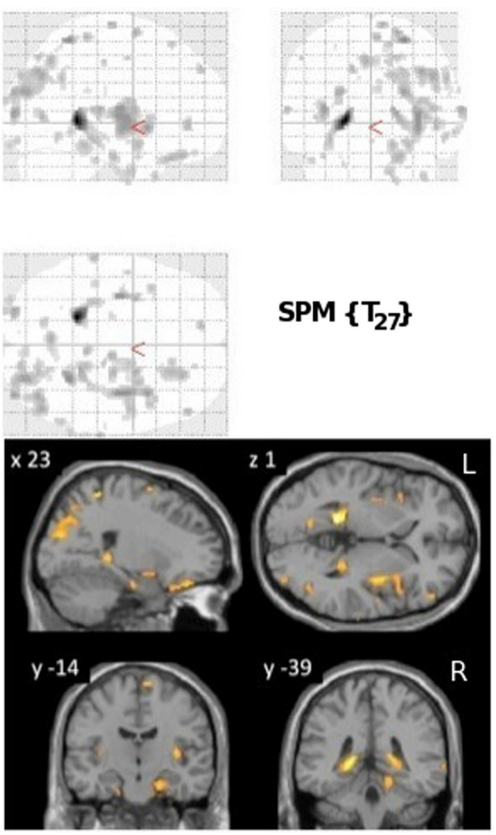

FIGURE 1 | Results of the univariate linear regression of VRLT error score with GM density. *Above panel*: glass brain; *below panel*: selected slices projected onto a single subject template. The slice labeled "$y = -39$" best illustrates the bilateral isthmus/retrosplenial lesion.

Metabolism (FDG) correlations

Normalized FDG radioactivity concentration correlation with VRLT performance identified a confluent region spanning right posterior cingulate, retrosplenial cortex, precuneus, lateral posterior parietal cortex, and posterior PHG. A less extensive and less significant cluster was seen on the left side involving posterior parietal cortex (**Figure 2**).

Diffusion (WM) correlations

VRLT performance correlated with λ_1 bilaterally in the WM of the cingulum bundle in the posterior cingulate/retrosplenial region. On the right side this was more extensive and confluently extended rostrally in the PHG to the level of the hippocampal head in the *y*-plane (**Figure 3**). RD, MD, and FA failed to produce confluent results in any tract.

MULTIVARIATE ANALYSES

Using GM density within an SVR model to predict VRLT performance did not produce values that correlated significantly with the true values (2-tailed $p = 0.19$). There was a significant predictive correlation between actual and predicted VRLT performance using normalized FDG radioactivity concentration (2-tailed $p < 0.005$). This involved bilateral postero-lateral parietal and retrosplenial cortices as well as right caudate nucleus, right mediodorsal thalamus and a small area of right dorso-lateral prefrontal cortex. Overall, the regression was more extensive in the right hemisphere (**Figure 4**). Plotting the results of the SVR found that one data point was a potential outlier, re-running the correlation with this data point excluded diminished the significance of the correlation (1-tailed $p = 0.05$) (**Figure 5**).

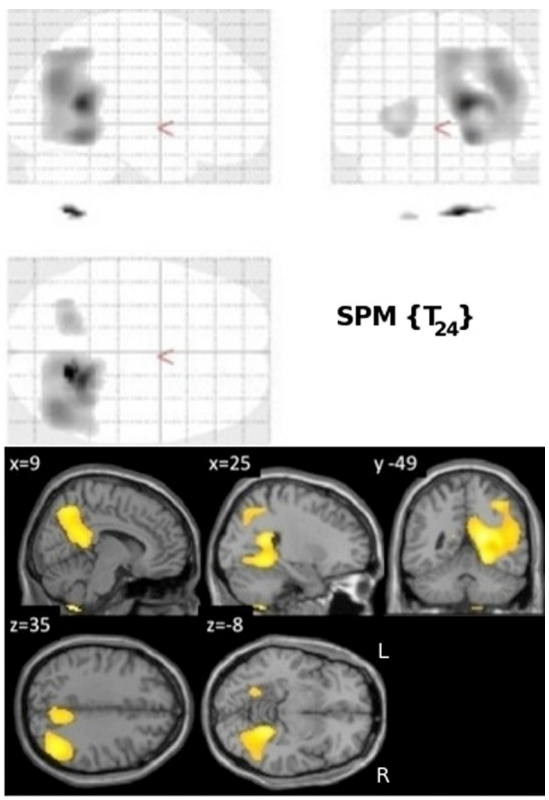

FIGURE 2 | Results of the univariate linear regression of VRLT error score with FDG metabolism. *Above panel*: glass brain; *below panel*: selected slices projected onto a single subject template.

CONVERGENCE OF RESULTS ACROSS METHODS AND MODALITIES

The univariate analyses of GM and FDG and the multivariate FDG analysis identified a common area of correlation in the right retrospenial cortex/isthmus region extending to the region of the hippocampal tail. Axial diffusion (λ_1) in WM adjacent to this region was also significantly correlated (**Figure 6**).

DISCUSSION

Performance on the VRLT, in which subjects attempt to learn routes in a virtual environment, was recently shown to have exquisite sensitivity for detecting impairment in very early AD; it also showed excellent ecological validity in that it correlated strongly with real world endorsements of route-finding difficulty (Pengas et al., 2010b). Univariate analyses of GM density, FDG (glucose metabolism) and WM axial diffusion found convergent correlations with the right retrosplenial/isthmus/posterior cingulate/hippocampal tail region. The multivariate analysis of FDG yielded a more distributed network of correlation that included this same region as well as lateral parietal association cortex, right caudate nucleus, and right dorso-medial thalamus. With the exception of the lateral parietal and retrosplenial regions, the network was exclusively right-sided. Though the present results offer considerably more detail, they are in general agreement with the GM density region of interest results of deIpolyi et al. (2007) who reported greater right side atrophy in AD and MCI patients who got lost, and involvement of the extreme right hippocampal tail (n.b. their region of interest analysis included hippocampi, parahippocampal gyri, and inferior parietal lobules).

Correlation of topographical memory impairment with the retrosplenial region is in agreement with behavioral data from focal lesions to this region (Takahashi et al., 1997; Maeshima et al., 2001). Similarly, functional neuroimaging studies of healthy subjects navigating in virtual environments activate the retrosplenial region (Ghaem et al., 1997; Maguire et al., 1998; Maguire, 2001; Ino et al., 2002; Wolbers et al., 2004). It also resonates with the observation that this area is the earliest detectable hypometabolic region in the MCI-stage of AD (Nestor et al., 2003b). The present findings suggest that this lesion is a significant contributor to the emergence of memory impairment in AD. Furthermore, the observation that both metabolism and GM density in this region correlated with VRLT performance suggests that this is not just a functional lesion but, rather, a direct consequence of local neurodegeneration. The correlation with axial diffusion in the WM subtending this region would also be consistent with local degeneration causing disruption to axonal projections from this area. As already mentioned, however, the diffusion analysis should only be treated as exploratory at this time; none of the other diffusion metrics correlated with VRLT performance, and, at present, too little is known about the dynamics of change between specific diffusion metrics and axonal loss to have strong expectations for how these variables may relate to each other.

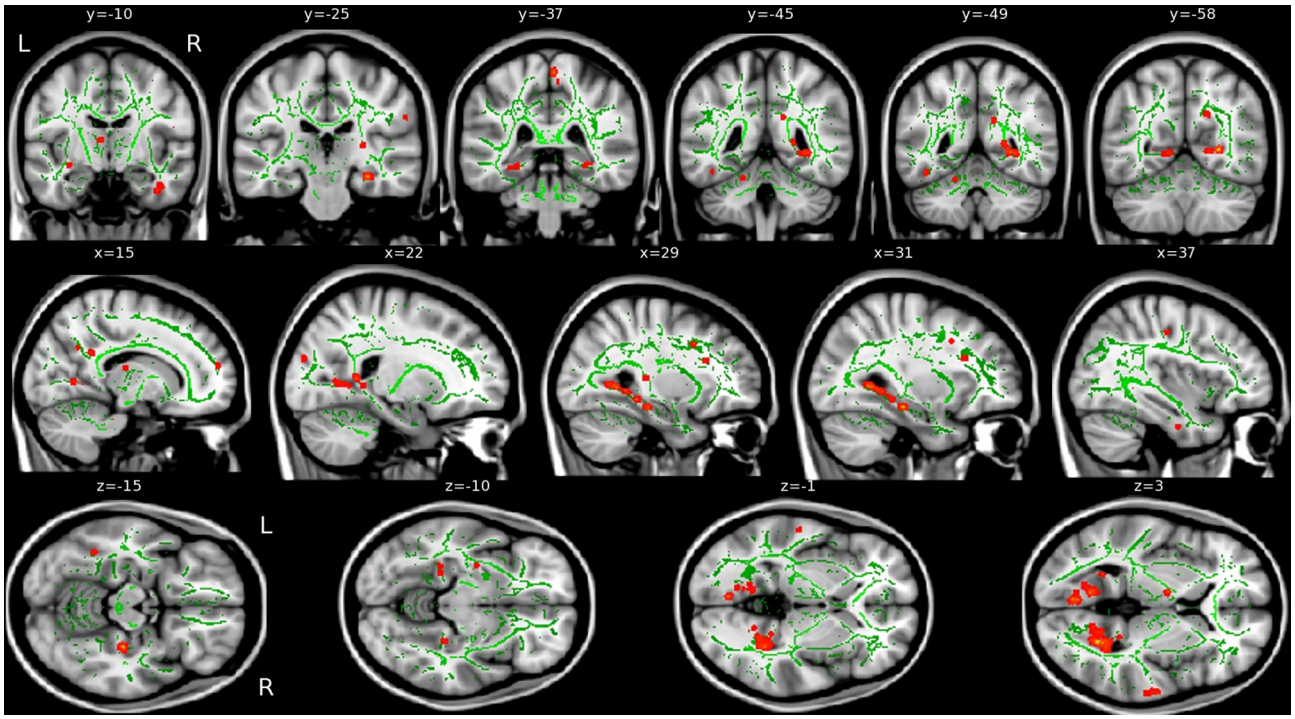

FIGURE 3 | Areas of correlation between increased axial diffusion (λ_1, red) and VRLT error score. The TBSS "skeleton" (i.e., the white matter tract centers on which the statistics are computed) is green.

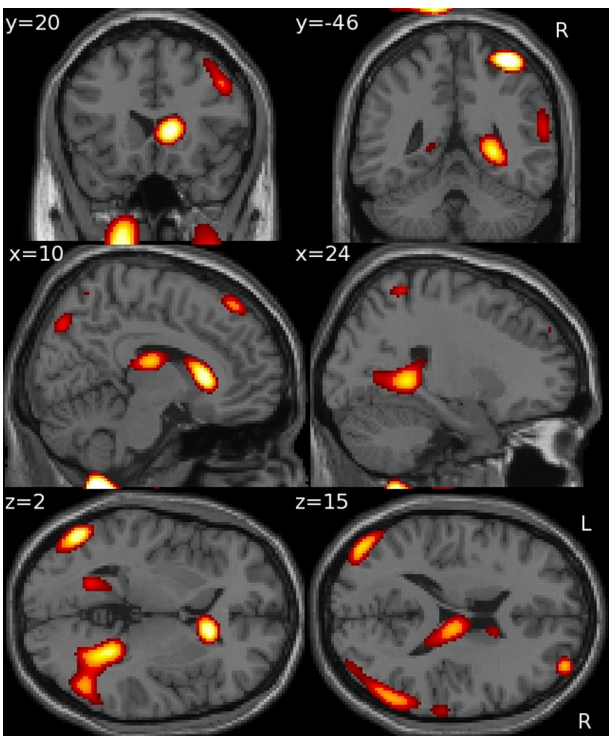

FIGURE 4 | Multivariate support vector regression of VRLT performance with normalized FDG metabolism.

The multivariate SVR analysis which estimates a significance level to the pattern of cerebral correlates as whole, and therefore could be viewed as giving a more informed picture of network level change, yielded a more complex picture than the mass univariate approach with respect to FDG. In addition to the retrosplenial lesion, this analysis revealed that lateral parietal regions—with a right-sided predominance—were also significantly related to VRLT performance. These findings highlight the homology between the fMRI pattern of activation during navigation (Ghaem et al., 1997; Maguire et al., 1998; Mellet et al., 2000; Burgess et al., 2001; Wolbers et al., 2004; Moffat et al., 2007) and the imaging profile in AD (Minoshima et al., 1997; Baron et al., 2001; Chetelat et al., 2002; Scahill et al., 2002; Nestor et al., 2003b; Acosta-Cabronero et al., 2010; Pengas et al., 2010a) that was the inspiration for developing this test. The analysis also highlighted right medio-dorsal thalamus in the correlation with VRLT performance. This location has not been a major feature of the spatial memory network in fMRI studies. Lesions to the thalamus are, however, an established cause of human amnesia (Stuss et al., 1988; Hodges and McCarthy, 1993) and, moreover, this area is part of the limbic-diencephalic network that is specifically hypometabolic in the amnesic prodrome of AD (Nestor et al., 2003a).

The failure to detect a significant network correlate with the multivariate GM SVR might suggest that the metabolic findings are predominantly physiological and separate from local degeneration (atrophy). It is important to emphasize, however, that this quite likely reflects the far greater sensitivity of FDG to detect local

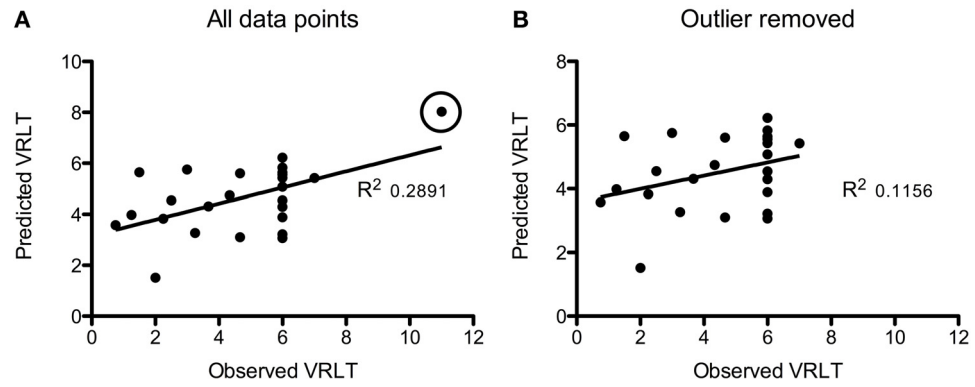

FIGURE 5 | Plots of the Support Vector Regression (predicted versus observed VRLT score). (A) Shows the full cohort: note that one data point (circled) appeared to be a potential outlier. Removing this data point **(B)** diminished the strength of the correlation though it remained significant ($p = 0.05$).

degeneration compared to GM density measurements. This phenomenon can be illustrated by contrasting the findings from two studies of the posterior cortical atrophy form of AD—one that examined glucose metabolism (Nestor et al., 2003c) and another that examined GM density (Whitwell et al., 2007). The lesion distribution in the two studies was identical suggesting a tight concordance between cerebral metabolism and atrophy; the key difference was that the FDG-PET result was generated from 16 subjects ($n = 6$ patients; $n = 10$ controls) whereas the GM density result came from 76 subjects ($n = 38$ in both patient and controls groups).

One finding in the multivariate FDG analysis probably does, however, represent a physiological network co-variance—this being the striking emergence that the right caudate nucleus was exerting an influence on performance. The right caudate nucleus is the one region identified to be part of the spatial memory network that is not a prominent component of the landscape of early degeneration in AD. It is, however, specifically activated during egocentric spatial memory tasks in healthy volunteers (Maguire et al., 1998; Doeller et al., 2008), and so would be expected to engage in a route learning test. Furthermore, there seems no reason to expect any disease-related caudate metabolism alterations in AD to be strongly right lateralized. We, therefore, propose that the unilateral right caudate finding in the current study offers direct evidence that this region is co-varying with posterior cortical regions involved in topographical memory performance. This observation reinforces the findings of previous fMRI studies in healthy volunteers that the right caudate nucleus is intimately involved in topographical memory processing using the complimentary model of a neurodegenerative disease that impairs this ability.

A very relevant negative in this study was the absence of prominent hippocampal correlation with task performance. Some analyses identified involvement of the extreme tail of the hippocampus, though, even then, it was never restricted to the hippocampus and could possibly have even been arising from correlation with neighbouring structures. Nevertheless, if real, it would be consistent with fMRI evidence that the tail may be the critical hippocampal component in spatial memory (Doeller et al., 2008). Arguably the more important point was that excluding the caudal couple of millimeters, no evidence was identified for hippocampal involvement in a topographical memory task that was previously shown to be highly sensitive to early AD. Without the current analyses, it is likely that many would assume topographical, indeed any kind of, memory test impairment in AD was a consequence of hippocampal damage. The present results challenge this view as an oversimplification. It would be overstating the case to suggest that the degree of hippocampal degeneration found in early AD is irrelevant to memory impairment—even in the present study it is possible that it exerted an influence that failed to reach statistical significance. It is, however, worth reflecting that the evidence that hippocampal degeneration causes memory impairment in AD is largely biased by the fact that studies finding correlation between these variables in the past have typically not examined regions beyond the MTL. Although many such studies found significant correlations (Kohler et al., 1998; de Toledo-Morrell et al., 2000a,b; Grundman et al., 2003; Reitz et al., 2009; Stoub et al., 2010), given that both MTL degeneration and memory impairment are a function of disease severity, one could ask, how could they fail to correlate? This risk of non-causal correlation is exemplified in studies in which non-mnemonic functions such as naming (Wilson et al., 1996) also correlated with MTL degeneration. The present results also offer explanation for the observation that patients with the non-Alzheimer disorder, semantic dementia, can perform the VRLT normally (Pengas et al., 2010b) yet have been previously shown to have greater MTL degeneration than is seen in AD (Chan et al., 2001; Galton et al., 2001; Nestor et al., 2006).

In conclusion, this study sought to investigate the neural basis of topographical memory impairment in AD. The traditional mass univariate regression approach employed with several different imaging modalities found correlations that particularly converged on a region encompassing retrosplenial/isthmus/posterior cingulate cortex and possibly hippocampal tail. A relatively novel multivariate approach, however, revealed that a, predominantly

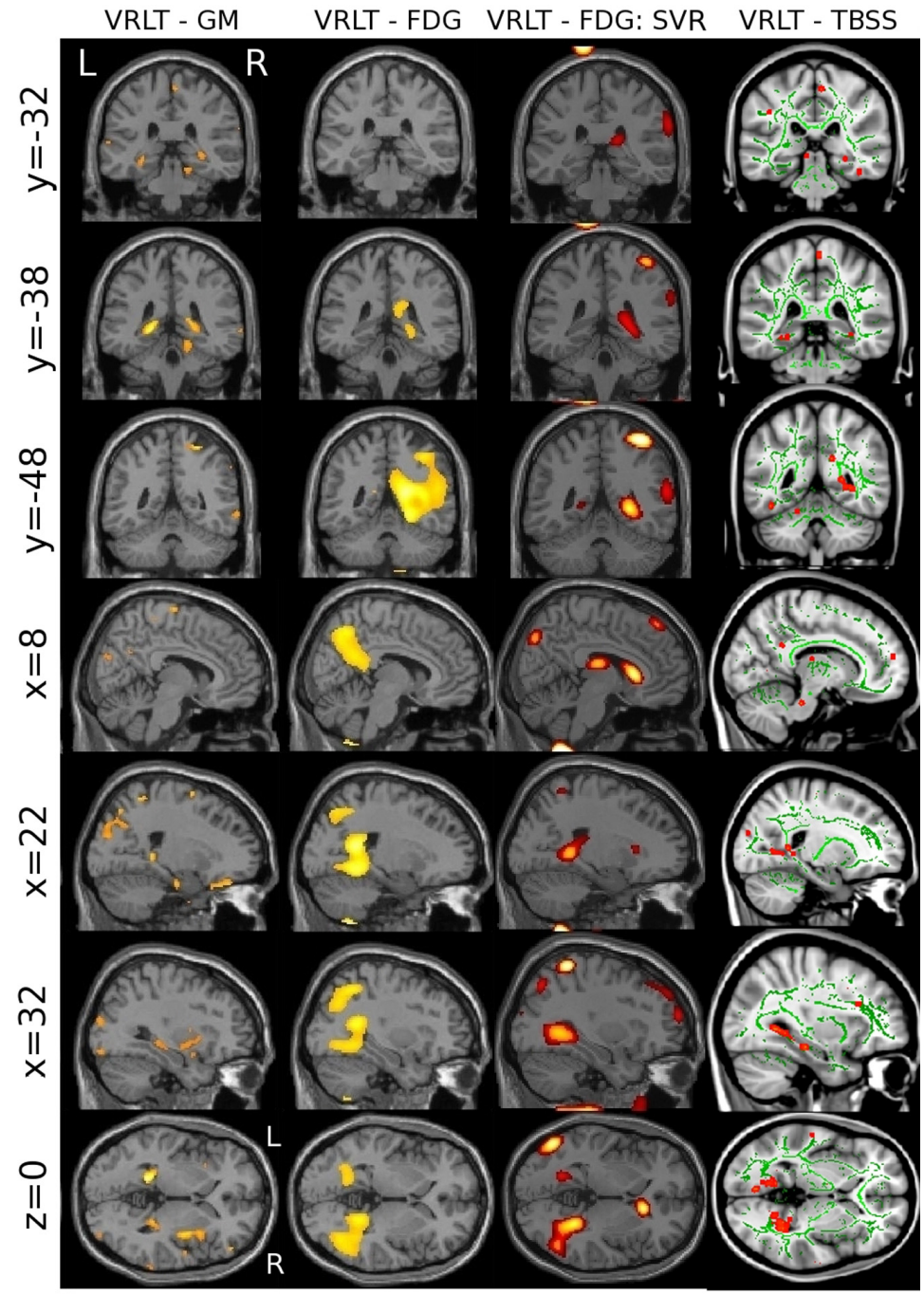

FIGURE 6 | Convergence of results across different imaging modalities and analysis techniques. Note that the retrosplenial/isthmus correlation is common to all analyses (see rows $y = -38$ and $z = 0$).

right hemispheric, network that reflected elements of (1) the limbic-diencephalic network known to be abnormal in incipient AD and (2) the topographical network highlighted in past fMRI studies of healthy volunteers, underpinned task performance in AD. These results, therefore, offer lesion evidence to corroborate observations made in healthy subjects regarding human route learning. Moreover, the findings highlight that memory impairment in AD is network-driven and unlikely to be simply a consequence of MTL damage.

ACKNOWLEDGMENTS

This work was supported by funding from the Medical Research Council UK, Alzheimer's Research UK and the Cambridge Biomedical Research Centre.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 27 March 2012; paper pending published: 23 April 2012; accepted: 12 June 2012; published online: 04 July 2012.

*Citation: Pengas G, Williams GB, Acosta-Cabronero J, Ash TWJ, Hong YT, Izquierdo-Garcia D, Fryer TD, Hodges JR and Nestor PJ (2012) The relationship of topographical memory performance to regional neurodegeneration in Alzheimer's disease. Front. Ag. Neurosci. **4**:17. doi: 10.3389/fnagi.2012.00017*

frontiers in
AGING NEUROSCIENCE

MINI REVIEW ARTICLE
published: 21 June 2012
doi: 10.3389/fnagi.2012.00016

Spatial navigation—a unique window into physiological and pathological aging

Ivana Gazova[1,2], Kamil Vlcek[2,3], Jan Laczó[1,2], Zuzana Nedelska[1,2], Eva Hyncicova[1], Ivana Mokrisova[1], Katerina Sheardova[2] and Jakub Hort[1,2]*

[1] Department of Neurology, Memory Disorders Clinic, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague 5, Czech Republic
[2] International Clinical Research Center and St. Anne's University Hospital Brno, Brno, Czech Republic
[3] Department of Neurophysiology of Memory, Institute of Physiology Academy of Sciences of the Czech Republic v.v.i., Prague, Czech Republic

Edited by:
Thomas Wolbers, University of Edinburgh, UK

Reviewed by:
Jacques Micheau, University of Bordeaux 1, France
Jose-Vicente Lafuente, University of Basque Country, Spain

****Correspondence:***
Ivana Gazova, Department of Neurology, Memory Disorders Clinic, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, V Uvalu 84, Prague 5, 150 06, Czech Republic.
e-mail: ivana.gazova1@gmail.com

Spatial navigation is a skill of determining and maintaining a trajectory from one place to another. Mild progressive decline of spatial navigation develops gradually during the course of physiological ageing. Nevertheless, severe spatial navigation deficit can be the first sign of incipient Alzheimer's disease (AD), occurring in the stage of mild cognitive impairment (MCI), preceding the development of a full blown dementia. Patients with amnestic MCI, especially those with the hippocampal type of amnestic syndrome, are at very high risk of AD. These patients present with the same pattern of spatial navigation impairment as do the patients with mild AD. Spatial navigation testing of elderly as well as computer tests developed for routine clinical use thus represents a possibility for further investigation of this cognitive domain, but most of all, an opportunity for making early diagnosis of AD.

Keywords: spatial navigation, physiological ageing, pathological ageing, mild cognitive impairment, Alzheimer's disease, allocentric navigation, egocentric navigation

INTRODUCTION

Spatial navigation is the ability to determine and maintain a route from one place to another (Gallistel, 1990). It consists of phylogenetically old cognitive functions allowing animals and humans to remember important locations and their mutual relations as well as their relation to the organism itself. Spatial navigation deficits are frequently observed in older population with a significant influence on the quality of life. Spatial navigation difficulties can represent the first sign of Alzheimer's disease (AD) development. The recent trend of spatial navigation research relies on tests translated from animal experiments, e.g., the human analog of the Morris Water Maze (MWM), used for clinical examination of people at risk of AD. In this article we summarize findings on spatial navigation changes in the physiological and pathological ageing and their practical significance for the early diagnosis of AD. As many neuropsychological tools still evoke controversies regarding the accuracy of detecting AD in its predementia stages, it is important to design a battery of tests, including spatial navigation testing for improving early diagnosis of AD.

PHYSIOLOGICAL AND PATHOLOGICAL AGEING

Physiological ageing is associated with structural and functional changes, mainly in the prefrontal cortex (Cabeza et al., 1997; Resnick et al., 2003) and to a lesser extent in the hippocampus (Jack et al., 1998; Grady et al., 1999), these are mirrored by changes in cognitive functions. Age-related changes in cognition include mild decline in attention, executive functions, working memory, and free memory recall, while other functions such as visuospatial functions, language, and semantic memory remain generally preserved for a long time (Park, 2000).

Pathological ageing is caused by underlying vascular or neurodegenerative diseases leading gradually to a dementia syndrome, where AD is the most common cause. The hallmark of AD is medial temporal lobe (MTL) atrophy including the hippocampus and the enthorinal cortex (Jack et al., 1997). Some recent studies on patients with AD suggested that atrophy is unequally distributed even within the hippocampus being most pronounced in the CA1 subfield compared to hippocampal atrophy pattern in normal ageing, where the CA1 subfield is relatively spared (Frisoni et al., 2008; Mueller and Weiner, 2009). The CA1 atrophy in patients with mild cognitive impairment (MCI) can even predict conversion to dementia due to AD (Chételat et al., 2008; Devanand et al., 2012). Besides the MTL structures, the precuneus was shown to be impaired very early even in presymptomatic AD (Scahill et al., 2002). With the disease progression, structures beyond MTL including lateral temporal, parietal and frontal cortices become affected (Braak and Braak, 1991). The first clinical sign of AD is usually the insidious onset of episodic memory impairment caused by neuropathological changes in MTL. Early in the course of the disease, memory impairment is followed by executive dysfunction together with impairment of working memory and attention. Later on, other cognitive domains including praxis, visuo-constructive skills, and language become affected, which reflects the spreading of the pathology further to the neocortex (Kertesz et al., 1986; Baudic et al., 2006). Proceeding cognitive impairment leads to a decline in every day functional abilities, which constitutes an important criterion for the diagnosis of the dementia syndrome.

In recent years, increasing attention has been paid to the mild end of the cognitive spectrum encompassing a transient

zone between the normal ageing and dementia, caused most frequently by AD. This transitional zone has been described by the term MCI (Petersen et al., 1999). The concept of MCI refers to a group of individuals who have some cognitive impairment yet of insufficient severity to constitute dementia due to a very slight degree of functional impairment. The individuals with MCI form a heterogeneous group. Those with memory impairment (amnesia) present amnestic MCI (aMCI), those with the non-memory domain impairment (i.e., executive functions, language, and visuo-spatial skills) present non-amnestic MCI (naMCI) (Petersen et al., 2001). Further sub-classification of both MCI subtypes is based on the number of affected cognitive domains. Isolated memory impairment represents aMCI single domain (aMCIsd), similarly, single non-memory domain impairment represents naMCI single domain (naMCIsd). Impairment in additional domains to these two subtypes assigns to aMCI multiple domain (aMCImd), or naMCI multiple domain (naMCImd). Individuals with aMCI subtype have a high risk of AD development; while those with naMCI subtype have a higher probability of progressing to non-AD dementias such as dementia with Lewy bodies, frontotemporal or vascular dementia. The risk of progression from MCI to dementia, particularly to AD, is not uniform and varies across epidemiological studies (Tierney et al., 1996; Petersen et al., 1999; Morris et al., 2001). The average rate of conversion is estimated to 12% per year (Petersen and Morris, 2003). In contrast, in healthy elderly subjects the rate of conversion to dementia is about 1–2% per year (Petersen et al., 1999).

Although aMCI patients represent at-risk population for AD development, this population is somewhat heterogeneous as it encompasses also individuals who will never progress to dementia. Lately, much effort is spent to identify the high risk patients with underlying AD pathology already in this prodromal (predementia) stage of the disease. For identification of prodromal AD patients, a combination of neuropsychological tests with various biomarkers is used. These include structural and functional neuroimaging, focused on the hippocampus and related structures (Small et al., 1999; Visser et al., 1999; Desikan et al., 2010), magnetic resonance spectroscopy (Modrego et al., 2011), cerebrospinal fluid assessment of amyloid-β peptide, tau and phosphorylated tau proteins (Hulstaert et al., 1999; Shaw et al., 2009), and amyloid labeling PET ligands (Resnick et al., 2010). Among neuropsychological tools, specific memory tests play an important role for identification of memory profile characteristic for AD that is present already in the predementia stages (Sarazin et al., 2007)—"amnestic syndrome of the hippocampal type" (Dubois and Albert, 2004). This syndrome forms a clinical core of the revised research diagnostic criteria for AD (Dubois et al., 2007) and is characterized by decreased memory recall despite controlled encoding and using of facilitation retrieval techniques (cueing or recognition) (Dubois, 2000). The MCI individuals with amnestic syndrome of the hippocampal type (HaMCI), compared to those with the amnestic syndrome of the non-hippocampal type (NHaMCI), form the major at-risk subgroup of MCI population (Sarazin et al., 2007) for the development of dementia due to AD. Although the tests designed to detect hippocampal amnestic syndrome (Grober et al., 1988) were shown to reflect atrophy of the hippocampus, especially its CA1 subfield (Sarazin et al., 2010), it still remains controversial, whether these tests are superior to other tests for the detection of early stage dementia (de Jager et al., 2010; Carlesimo et al., 2011). The uncertainty about the usefulness of cued recall as a diagnostic tool for MCI and AD is expressed also in the National Institute on Aging and the Alzheimer's Association guidelines (Albert et al., 2011; McKhann et al., 2011), which take into account symptoms of patients with predominant parietal atrophy.

Recent studies indicate that there is a promising chance that, spatial navigation tests reflecting MTL damage may identify patients with AD already in the prodromal stages (Laczó et al., 2009).

SPATIAL NAVIGATION STRATEGIES AND ITS MORPHOLOGICAL CORRELATES

While navigating through the environment, people can use two basic navigation strategies associated with distinct internal representations of space. The egocentric navigation is body-centered strategy that utilizes distances and directions to or from individual landmarks with respect to the subject's body position. The allocentric navigation is a world-centered strategy using information about distances and angles between different locations in the environment independent of the position of the subject.

Animal research yielded valuable information about the role of MTL in the processes of spatial navigation (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978; Morris et al., 1982). A key structure of the allocentric navigation is the hippocampus, especially its CA1 subfield (Brun et al., 2008). In 1971 O'Keefe and Dostrovsky discovered specific place-firing cells in the hippocampus of the rat (O'Keefe and Dostrovsky, 1971). These findings supported the theory of a cognitive map (Tolman, 1948) and the dissociation between the egocentric and allocentric navigation strategies. Experiments in the MWM demonstrated spatial navigation impairment in the rats after hippocampal lesion (Morris et al., 1982). Hippocampus is crucial for consolidation, encoding, and long term storage of spatial information (Squire, 1992). The association of hippocampus with allocentric navigation in humans has been demonstrated in various studies in real-space and virtual environments (Maguire et al., 1998; Astur et al., 2002). In one study, Holdstock et al. (2000) tested patient (YR) with selective bilateral hippocampal lesion for recall of visuospatial information and found that YR was more impaired at recalling allocentric than egocentric information. More specifically, right CA1 hippocampal subfield seems to be involved in encoding of allocentric spatial information in humans (Suthana et al., 2009). There is evidence that egocentric information is processed outside of the hippocampal system (O'Keefe and Nadel, 1978), in the parietal cortex including precuneus and the caudate nucleus (Mountcastle et al., 1975; Maguire et al., 1998). Lesions of the right posterior parietal cortex are characterized by an egocentric orientation deficit (Kase et al., 1977; Levine et al., 1985; Stark et al., 1996).

SPATIAL NAVIGATION IMPAIRMENT IN PHYSIOLOGICAL AND PATHOLOGICAL AGEING

Spatial navigation has been thoroughly studied in animal models. Navigational tasks based on the models of MWM (Morris, 1981)

were used in testing rats of different age (Ingram, 1988; McLay et al., 1999; Begega et al., 2001). Results of these studies suggested age-related deficit of navigational abilities in aged rodents and inspired translational research of spatial navigation in humans. Studies in different environments compared healthy elderly persons with younger adults. Significant deficits in learning a route through a hospital lobby was described in participants 60 years and older, with a tendency to be impaired even in participants in their 50s (Barrash, 1994). Several studies suggested that elderly people have lower cognitive capacity limits in temporospatial processing. In one experiment using series of slides of unfamiliar neighborhood, elderly adults recalled landmarks by their saliency and non-spatial associations rather than by their spatial relationships (Lipman, 1991). However, many other studies emphasized deficits specifically in spatial configuration memory and in place navigation in aged population. Wilkniss et al. (1997) let participants undergo navigational tasks in university building and found that older persons made more errors than their younger counterparts in temporal ordering of landmarks, in recalling the learned route, and in using the learned map in navigation. These deficits suggest a lower ability to use a configural spatial representation to navigate. Another study showed navigational difficulties of healthy elderly while driving a car leading to avoidance of unfamiliar places and routes and thus limiting their mobility (Burns, 1999). Human analog of the MWM was developed in an effort to transform navigational tasks into laboratory conditions. It was employed in a study that demonstrated impairment in acquisition and use of the cognitive map of the maze in the group of elderly participants (Newman and Kaszniak, 2000). Moffat and Resnick (2002) were among the first authors implementing the use of virtual reality in testing of spatial navigation. They compared performance of elderly and younger individuals in the virtual analog of MWM and found deficit of place learning using room-geometry cues in the group of older participants. Furthermore, they suggested that allocentric impairment may contribute to age-related deficit of spatial navigation. This hypothesis was later supported by the study of Iaria and colleagues, according to which the older participants are less effective in forming and using the cognitive maps of an environment (Iaria et al., 2009). A recent study examined age-related differences in strategy preference and found a shift toward egocentric navigation strategy in older participants, which may reflect an adaptation mechanism for the hippocampal dysfunction (Rodgers et al., 2012). Studies correlating hippocampal volume with spatial navigation performance in cognitively healthy elderly provided however contradicting results, with some of them documenting positive correlation (Driscoll et al., 2003; Head and Isom, 2010) and other reporting no association (Moffat et al., 2006; Nedelska et al., 2012).

Spatial navigation impairment occurs early in AD (Monacelli et al., 2003; Pai and Jacobs, 2004); reports about spatial deficits such as getting lost in familiar places and other can in many cases lead to diagnosis of dementia (Klein et al., 1999). The combination of visual perception and memory deficits is probably the mostly defining factor of spatial disorientation in patients with AD (Henderson et al., 1989), where both allocentric and egocentric navigation strategies are impaired (Hort et al., 2007; Weniger et al., 2011). According to several studies, these general spatial deficits in AD seem to be linked mainly to impairment of visual motion processing (Kavcic et al., 2006). Nevertheless, spatial navigation impairment can be detected even before the development of the full blown dementia syndrome, in the stage of MCI (Mapstone et al., 2003; deIpolyi et al., 2007; Hort et al., 2007; Laczó et al., 2011). Given that aMCI is associated with a higher risk of progression to AD, the current research of spatial navigation has focused on this group of patients. A visuospatial subtype of aMCI with impaired radial motion perception indicating spatial perception deficit was identified in one of the first studies in this field (Mapstone et al., 2003). Spatial navigation impairment was documented in aMCI patients performing a route-learning task in the hospital lobby (deIpolyi et al., 2007). In this study, the patients, who made at least one error on the road, did not differ in neuropsychological tests from those with no errors on the road, but they had lower right MTL and posterior parietal cortex volumes that probably underlie spatial navigation deficit. Temporal order spatial memory was recently suggested as another cognitive marker of AD and aMCI (Bellassen et al., 2012). Remembering a sequence of three turns in a simple maze distinguished well between AD, healthy older subjects, and group of patients with frontotemporal lobe degeneration. Spatial navigation impairment is present even in patients with isolated memory deficit aMCIsd (Hort et al., 2007). The patients with aMCIsd tested in the real-space human version of the MWM had an isolated impairment of allocentric navigation, suggesting spatial memory impairment due to MTL dysfunction. On the other hand, the patients with aMCImd had more general spatial navigation impairment in both, allocentric and egocentric strategies, indicating that structures beyond MTL, presumably the parietal cortex, are affected in this group (Hort et al., 2007). Consistent with these findings patients with aMCI were impaired in both egocentric and allocentric strategies in a study using virtual reality environment, where right precuneus volume was associated with egocentric navigation performance (Weniger et al., 2011). Further study examined spatial navigation in a real-space human version of MWM and found more profound spatial navigation deficit in the HaMCI group in comparison to the NHaMCI group, especially in allocentric navigation, which corresponds with the probable hippocampal dysfunction (Laczó et al., 2009). In addition, the HaMCI group resembled the AD group in spatial navigation performance thus indicating that spatial navigation deficit in the HaMCI may be the first sign of incipient AD. In the same vein, in another study using real-space human analogy of MWM (Nedelska et al., 2012), right hippocampal volume in aMCI and AD patients was associated with an allocentric navigation performance. Thus testing of the allocentric navigation, targeting hippocampus and its CA1 subfield (Suthana et al., 2009), and egocentric navigation, focusing more on posterior parietal cortex and precuneus, could be a useful method of recognizing the aMCI patients at higher risk of AD.

Virtual analogs can probably substitute the real space environment in estimating the navigational deficits of MCI and AD patients, as implied by two recent studies. In an experiment consisting of learning a route through a hospital lobby and of a follow-up spatial tests series, strong correlation was found across all subject groups between the total spatial score from the

real hospital lobby and the total score from its virtual analog (Cushman et al., 2008). Similarly, high correlation was found in another study between scores in a real-space human version of MWM and its virtual 2D analog on a computer monitor representing the circular space as from above (Laczó et al., 2012). These results suggest that computer analogs of real space tests can yield measures of broad applicability to early detection of navigational impairment in MCI or AD.

CONCLUSION

In the course of physiological ageing, there is a selective mild decline of spatial navigation. Particularly allocentric navigation is impaired, which may be a consequence of the age-related deficits in mediotemporal functioning observed in the elderly. AD is associated with the development of characteristic pathological changes in the brain, especially in the hippocampus and its CA1 subfield, that further spread to parietal cortex, including precuneus, and other areas as the disease progresses. The severe spatial navigation deficits demonstrated in patients in early stage of AD are caused by both hippocampal and parietal dysfunction. Those spatial navigation deficits can be detected even in the stage of MCI patients with amnestic syndrome of hippocampal types, who are at the highest risk of AD development, and who manifest with the spatial navigation deficit similar to that in AD. Therefore, spatial navigation testing could become a reliable tool of identifying patients in the prodromal stages of AD, before the development of dementia syndrome (Vlcek, 2011). Adding spatial navigation tests to neuropsychological batteries will increase the diagnostic accuracy and early detection of patients with AD in the predementia stages. Given that real-space testing is technically difficult, new methods of testing are being developed. 2D computer tests and virtual reality environments appear to be promising areas for extension of spatial navigation testing to the routine clinical use.

ACKNOWLEDGMENT

This work was supported by Grant Agency of the Czech Republic Grants 309/09/1053 and 309/09/0286; European Regional Development Fund—Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123); Internal Grant Agency of the Ministry of Health of the Czech Republic Grant NT11225-4; Ministry of Education, Youth and Sports of the Czech Republic Grants 1M0517 and LC554, and research project AV0Z50110509, Grant Agency of Charles University in Prague (No. 2120145) and Institutional Support of Laboratory Research Grant No. 2/2012 (699002).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 April 2012; paper pending published: 23 April 2012; accepted: 07 June 2012; published online: 21 June 2012.

*Citation: Gazova I, Vlcek K, Laczó J, Nedelska Z, Hyncicova E, Mokrisova I, Sheardova K and Hort J (2012) Spatial navigation—a unique window into physiological and pathological aging. Front. Ag. Neurosci. **4**:16. doi: 10.3389/fnagi.2012.00016*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 12 June 2012
doi: 10.3389/fnagi.2012.00014

Differential effects of aging on spatial learning through exploratory navigation and map reading

Naohide Yamamoto* and Gregory J. DeGirolamo

Department of Psychology, Cleveland State University, Cleveland, OH, USA

Edited by:
Thomas Wolbers, University of Edinburgh, UK

Reviewed by:
Scott Moffat, Wayne State University, USA
Jon Kelly, Iowa State University, USA

****Correspondence:***
Naohide Yamamoto, Department of Psychology, Cleveland State University, 2121 Euclid Avenue, Cleveland, OH 44115, USA.
e-mail: n.yamamoto@csuohio.edu

It has been shown that abilities in spatial learning and memory are adversely affected by aging. The present study was conducted to investigate whether increasing age has equal consequences for all types of spatial learning or impacts certain types of spatial learning selectively. Specifically, two major types of spatial learning, exploratory navigation and map reading, were contrasted. By combining a neuroimaging finding that the medial temporal lobe (MTL) is especially important for exploratory navigation and a neurological finding that the MTL is susceptible to age-related atrophy, it was hypothesized that spatial learning through exploratory navigation would exhibit a greater decline in later life than spatial learning through map reading. In an experiment, young and senior participants learned locations of landmarks in virtual environments either by navigating in them in the first-person perspective or by seeing aerial views of the environments. Results showed that senior participants acquired less accurate memories of the layouts of landmarks than young participants when they navigated in the environments, but the two groups did not differ in spatial learning performance when they viewed the environments from the aerial perspective. These results suggest that spatial learning through exploratory navigation is particularly vulnerable to adverse effects of aging, whereas elderly adults may be able to maintain their map reading skills relatively well.

Keywords: aging, spatial learning, navigation, map, ground-level, aerial, route, survey

1. INTRODUCTION

Abilities in spatial learning and memory are adversely affected by both normal and pathological aging. Many senior citizens experience great difficulty in navigation in unfamiliar environments (Burns, 1999), and it is often the case that topographical disorientation is among the earliest symptoms displayed by patients with Alzheimer's disease (Pai and Jacobs, 2004). Results from experimental studies have been consistent with these epidemiological observations, showing that elderly participants (either healthy or demented) performed worse than young participants in a variety of spatial learning and memory tasks (for review, see Iachini et al., 2009; Moffat, 2009; Vlček, 2011). In spite of these converging and accumulating findings in the literature, psychological mechanisms of this age-related decline are poorly understood. For example, it is largely unknown whether aging has equal consequences for all types of spatial learning or impacts certain types of spatial learning selectively. The objective of the present study was to address this issue by contrasting the effects of normal aging on spatial memories acquired through two major methods of spatial learning: exploratory navigation in a ground-level (also called *route*) perspective and map reading in an aerial (also called *survey*) perspective (Siegel and White, 1975; Thorndyke and Hayes-Roth, 1982).

Previous studies demonstrated age-related decrements of spatial learning both in exploratory navigation and in map reading. Extensive research has been carried out by having participants learn environments through exploratory navigation in the first-person (i.e., ground-level) perspective. Some studies involved real navigation in physical environments (e.g., Kirasic, 1991; Barrash, 1994; Wilkniss et al., 1997; Newman and Kaszniak, 2000; Iachini et al., 2005), and others utilized simulated navigation in virtual environments (e.g., Moffat et al., 2001; Moffat and Resnick, 2002; Lövdén et al., 2005; Iaria et al., 2009; Zakzanis et al., 2009; Liu et al., 2011). These studies commonly found that young participants acquired knowledge of the environments more accurately or quickly than senior participants (see also Cushman et al., 2008). Similarly, when participants learned specific routes on maps first and attempted to trace them in actual environments later, older adults were slower and less accurate (Wilkniss et al., 1997; Carelli et al., 2011). In addition, young adults tended to use maps more effectively for spatial learning than elderly adults: young adults recalled more landmark locations than elderly adults after studying street maps (Thomas, 1985; De Beni et al., 2006; Meneghetti et al., 2011), and having a map of an environment during exploratory navigation did not enhance elderly adults' learning of object locations (Sjölinder et al., 2005). All of these findings indicates that certain degrees of decline in spatial learning abilities take place in later life regardless of the ways in which an environment is learned. However, because spatial learning by exploratory navigation and spatial learning by map reading were examined separately in the previous studies, it remains unclear whether these two kinds of spatial learning show the same level of decline or one goes down more significantly than the other. Thus, the

present study was designed to make a direct comparison between exploratory navigation and map reading to investigate possible differential effects of aging on these two types of spatial learning.

Neuroimaging and neurological studies have provided important clues for addressing this issue. On one hand, neuroimaging studies have suggested that activation in the medial temporal lobe (MTL), hippocampus and parahippocampal cortex in particular, is a key to distinguishing spatial learning through exploratory navigation and spatial learning through map reading. For example, Shelton and colleagues found that encoding of spatial information through exploratory navigation and map reading elicited activations in overlapping areas of the young adult brain, but the MTL was activated more strongly by exploratory navigation than map reading (Shelton and Gabrieli, 2002; Shelton and Pippitt, 2007). When Borghesani et al. (2008) applied the same paradigm to healthy elderly adults who did not carry the apolipoprotein E ε4 allele, a known genetic risk factor for Alzheimer's disease (Strittmatter et al., 1993), they found that MTL activity during spatial learning through exploratory navigation but not through map reading was correlated with subsequent performance on a spatial memory test. Furthermore, when similar activations in the MTL were observed while participants learned environmental layouts in other studies, they typically learned environments through exploratory navigation (e.g., Aguirre et al., 1996; Grön et al., 2000; Moffat et al., 2006; Antonova et al., 2009; Iglói et al., 2010; Marchette et al., 2011; but see also Blanch et al., 2004). On the other hand, cross-sectional and longitudinal studies of age-related brain volume changes have revealed significant atrophy of the MTL in healthy elderly populations (Golomb et al., 1993; Jack et al., 1997, 1998; Šimić et al., 1997; Insausti et al., 1998; Jernigan et al., 2001; Scahill et al., 2003; Raz et al., 2004; but see also Sullivan et al., 1995, 2005). Importantly, this shrinkage of the MTL has actual behavioral consequences on spatial learning: Nedelska et al. (2012) demonstrated that smaller volume of the right hippocampus corresponds to larger impairment of spatial learning in the first-person perspective. Similarly, impaired performance of elderly adults in spatial learning through exploratory navigation correlated with reduced activation of the MTL, which might result from the atrophy of this brain region (Meulenbroek et al., 2004; Moffat et al., 2006; Antonova et al., 2009). Together, these neuroimaging and neurological findings lead to a hypothesis that vulnerability of the MTL to age-related atrophy makes spatial learning through exploratory navigation more susceptible to detrimental effects of increasing age. By contrast, because the MTL is engaged to a lesser extent while encoding spatial information from maps, it is also predicted that spatial learning through map reading would be affected by aging less significantly.

These hypotheses were tested in an experiment reported below. Young and senior participants learned locations of landmarks in virtual environments by viewing them either from a perspective of an observer walking through the environments (i.e., exploratory navigation) or from an aerial perspective that had a constant orientation relative to the environments (i.e., map reading). After learning each environment, they attempted to reproduce the layout of landmarks in a smaller scale. It was predicted that senior participants would reconstruct the layouts less accurately than young participants. More specifically, a greater difference between young and senior groups would be observed following spatial learning through exploratory navigation than that through map reading.

2. MATERIALS AND METHODS

2.1. PARTICIPANTS

Forty-eight participants gave their informed consent to participate in the experiment. They included 24 young participants (9 males and 15 females, 18–33 years old) and 24 senior participants (13 males and 11 females, 60–80 years old). Means (M) and standard deviations (SD) of their ages were as follows: $M = 21$, $SD = 4.76$ (young); and $M = 68.5$, $SD = 5.19$ (senior). The exact age of one young participant was not available. These two groups differed significantly in mean ages but not in ratios of males and females, $t_{(45)} = -31.95$, $p < 0.001$ and $\chi^2_{(1)} = 1.34$, $p = 0.25$, respectively. They received either monetary compensation or partial credit in a psychology course in return for their participation. They were native or fluent speakers of English and reported normal or corrected-to-normal vision.

All but one senior participant were enrolled in courses at Cleveland State University at the time of the experiment. Thus, although no formal screening was conducted, it was reasonable to assume that they were cognitively healthy individuals.

2.2. DESIGN AND PROCEDURE

The experimental protocol described below was approved by the institutional review board of Cleveland State University. Four virtual environments of the same size (110 × 130 ft in virtual space) were presented on the display of a desktop computer by using the PsyScope program (Cohen et al., 1993). They were visually distinct from each other (see **Figure 1** for examples), and each environment contained 10 large landmarks and seven small objects in a unique configuration. They were the same environments as those used in previous studies by Shelton and colleagues (e.g., Shelton and Gabrieli, 2002; Shelton and McNamara, 2004; Shelton and Pippitt, 2007). Each participant viewed all four environments, two from the perspective of a six-foot-tall observer walking through the environments (navigation condition; **Figure 1A**) and the other two from the perspective of an observer who was 70 ft above the ground and looking straight down (map condition; **Figure 1B**). In both conditions, approximately 2–3 landmarks were visible in their entirety at any given time (see **Figures 1A** and **B**). The walk-through of an environment in the navigation condition always began at the southwest corner and proceeded clockwise along the perimeter of the environment (**Figure 1C**). At each corner, the observer made a 90°-turn to face the new direction of travel. Viewing of an environment in the map condition was carried out in a similar manner. The observer was initially at the southwest corner and moved along four legs of the environment in the same direction. An important difference is that in the map condition the observer maintained the initial orientation (indicated by the arrow labeled as Leg 1 in **Figure 1C**) within each environment. Variable orientations and the fixed orientation were utilized in navigation and map conditions, respectively,

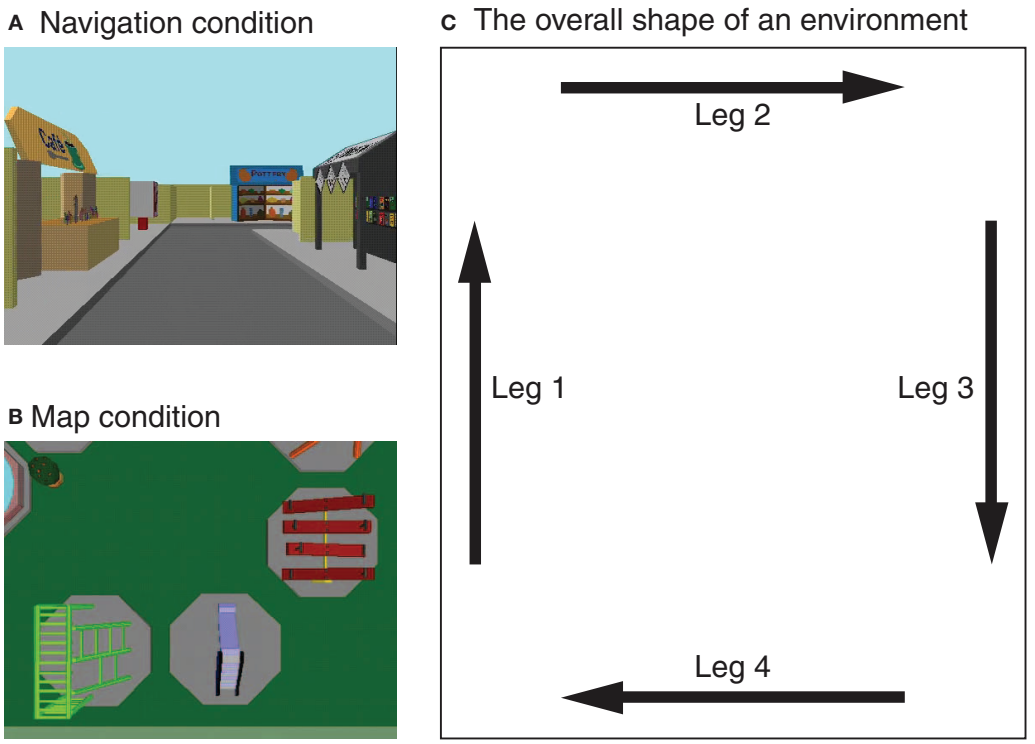

FIGURE 1 | Examples of virtual environments learned by participants in the experiment. They were presented either from a ground-level perspective in varying orientations **(A)** or from an aerial perspective in a fixed orientation **(B)**. The presentation of each environment began at its southwest corner (lower left corner in the figure) and proceeded clockwise along the four legs **(C)**. These virtual environments were originally created and used by Shelton and colleagues (Shelton and Gabrieli, 2002; Shelton and McNamara, 2004).

in order to capture essential aspects of corresponding types of spatial learning: exploratory navigation is conducted in the first-person perspective that varies with an observer, whereas maps are typically read in a single orientation (Shelton and Pippitt, 2007).

Participants were instructed to learn the locations of the 10 landmarks for a later memory test. They were given a diagram similar to **Figure 1C** and informed that they would view environments along the four legs in clockwise direction. They were also told that environments would be presented from either a ground-level or an aerial perspective. During the first run of each environment, an experimenter named 10 landmarks that were to be learned. Subsequently, participants viewed six additional runs of the environment by themselves. They were encouraged to pay close attention to all of the subsequent showings of the environment by naming the landmarks every time they appeared on the screen. To clearly indicate which leg they were in at any given moment, a label specifying a leg number was presented for 4 s right before each leg was shown. Each run of an environment took 56 s including the leg labels.

After learning each environment, participants were presented with a dry-erase board on which a rectangle representing the perimeter of the environment was drawn in scale (17.92 × 21.18 cm). It also specified the southwest corner (i.e., the starting point) of the environment and the direction of the first leg, which was aligned with participants' egocentric orientation at the time of initial presentation of the board. Participants were free to turn the board, if they so chose. They were given 10 identical magnet disks (2 cm diameter), which were to be placed at the locations of landmarks within the rectangle. They were also given names of the 10 landmarks and used them to indicate which disk represented which landmark. They were allowed to place the landmarks in any order and spend unlimited time to complete this task. No error feedback was given to participants.

Following completion of the memory test, participants were presented with a new environment in the same procedure. This study-test sequence was repeated until all four environments were learned and tested. The order of two perspectives was counterbalanced over participants. Four environments were randomly assigned to each perspective with the constraint that each environment appeared in each position of the sequence with equal frequency.

2.3. DATA ANALYSIS

The dependent measure was accuracy of the reconstructed layouts of landmarks. It was obtained through extension of bidimensional regression (Tobler, 1994). In this technique, a reconstructed layout first undergoes translation, rotation, and linear scaling so that it is transformed into the correct layout as much as possible. The best-fit layout can be uniquely determined by the least square method, and the regression coefficients associated with this transformation are converted into a distortion index (DI),

which reflects the overall accuracy of the reconstructed layout independent of translation, rotation, and scaling factors. The DI is a dimensionless value ranging from 0 to 100, with 0 indicating accurate reconstruction of the layout and 100 corresponding to the case in which all landmarks are placed in a single point. Details of the computational procedure are described by Waterman and Gordon (1984).

Although primary independent variables in this experiment were participant groups (young vs. senior) and types of spatial learning (navigation vs. map), it included an additional variable that was not relevant to the present study: once within each type of learning, the four legs of an environment were presented in random order. However, other than increasing the overall distortion of reconstructed layouts of landmarks, this variable showed virtually no interactions with group or learning type. Thus, this additional variable was not included in the analysis. Dropping this variable did not introduce any bias in results reported below because its effect was equally distributed across all conditions (i.e., the three variables were factorially combined).

3. RESULTS

DIs from the two environments learned in the same type of learning were averaged within each participant, and then their means and standard deviations were calculated for each age group and for each learning type. They were as follows (see also **Figure 2**): $M = 47.07$, $SD = 19.63$ (young, navigation); $M = 34.27$, $SD = 13.66$ (young, map); $M = 65.51$, $SD = 22.02$ (senior, navigation); and $M = 35.46$, $SD = 14.27$ (senior, map).

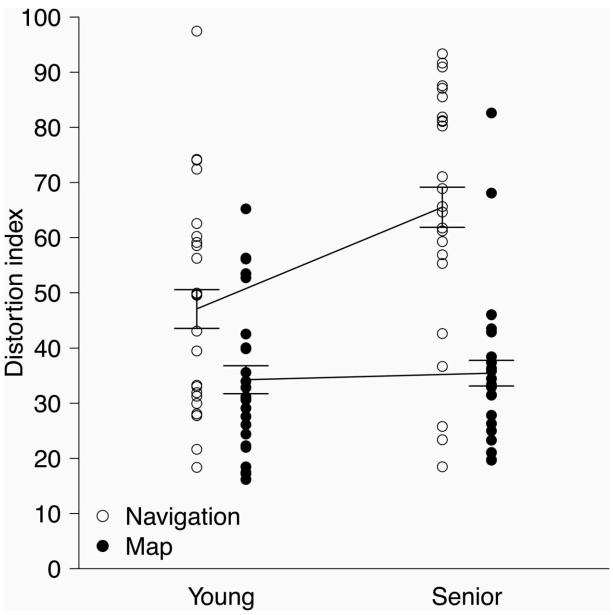

FIGURE 2 | Distortion indices (DIs) as a function of group (young vs. senior) and type of learning (navigation vs. map). Each dot shows a DI of one participant. For each type of learning, a solid line connects the means of the age groups. Error bars represent ±1 standard error of the mean.

Data were checked for outliers, but only one data point of a senior participant in the map condition fell outside the range of $M \pm 3$ *SD*, and excluding this participant did not alter the results at all. Thus, all data points were included in the analysis. DIs were subjected to a split-plot analysis of variance with group (young vs. senior) as a between-subject factor and type of learning (navigation vs. map) as a within-subject factor. Generalized eta squared (η^2_G) values are reported below as effect size statistics (Olejnik and Algina, 2003; Bakeman, 2005).

Figure 2 shows DIs as a function of group and learning type, revealing two major findings. First, following spatial learning through exploratory navigation senior participants created more distorted layouts of landmarks than young participants, but following spatial learning through map reading these two groups performed equivalently. Consistent with these observations, the interaction between group and learning type was significant, $F_{(1,\ 46)} = 7.54$, $p = 0.0086$, $\eta^2_G = 0.056$. Simple main-effect tests comparing the two age groups yielded a significant result within the navigation condition but not within the map condition, $F_{(1,\ 46)} = 12.40$, $p < 0.001$, $\eta^2_G = 0.21$, and $F_{(1,\ 46)} = 0.052$, $p = 0.82$, $\eta^2_G = 0.0011$, respectively. Additionally, this substantial worsening of senior participants' performance in the navigation condition made the main effect of group significant, $F_{(1,\ 46)} = 5.49$, $p = 0.024$, $\eta^2_G = 0.071$. Second, there was an overall difference in the quality of reconstructed layouts between navigation and map conditions: participants reproduced the layouts more accurately after spatial learning through map reading than that through exploratory navigation. This was indicated by the significant main effect of learning type, $F_{(1,\ 46)} = 46.56$, $p < 0.001$, $\eta^2_G = 0.27$. Furthermore, a simple main-effect test comparing the two conditions in the young group was also significant, $F_{(1,\ 46)} = 8.31$, $p = 0.0060$, $\eta^2_G = 0.15$, showing that accuracy of reproduced layouts was reliably different between navigation and map conditions even among young participants.

4. DISCUSSION

The present study was conducted to investigate whether increasing age has differential impacts on spatial learning through exploratory navigation in the first-person (i.e., ground-level) perspective and map reading in an aerial perspective. On the basis of previous findings that encoding of spatial information from the first-person perspective strongly engages the MTL and that this brain region is susceptible to age-related atrophy, it was hypothesized that elderly adults would be especially impaired at learning an environmental layout by navigating in the environment. Results from the experiment supported this hypothesis, showing that (1) senior participants constructed the layouts of landmarks less accurately than young participants after learning them through exploratory navigation; and (2) young and senior participants reproduced the layouts with equivalent accuracy after learning them through map reading. These data suggest that not all types of spatial learning are affected equally by aging. Rather, it is suggested that seniors' ability in learning environments from maps is better maintained through normal aging processes than their ability to acquire spatial knowledge from actual navigational experiences.

It is noteworthy that in the experiment young and senior participants performed equivalently after learning environments through maps. This suggests that the observed difference between the two age groups in the navigation condition cannot be explained entirely by general age-related factors such as slower speed of information processing and less familiarity with computers. In navigation and map conditions, the environments were presented at comparable rates (i.e., approximately the same number of landmarks were visible at any given time in both conditions), and identical learning and test procedures were employed. Furthermore, the competent performance of senior participants in the map condition supports the observation that they were cognitively healthy individuals. Thus, it is reasonable to conclude that the decreased accuracy of spatial memories in the navigation condition was indicative of specific effects of normal aging on spatial learning through exploratory navigation.

It is also important to note that although the present study found little difference between young and senior participants in the map condition, it does not necessarily indicate that there would be no age-related decline in map reading abilities. As discussed in the introduction, previous studies showed that elderly adults had a tendency to acquire spatial knowledge from maps less proficiently than young adults (Thomas, 1985; De Beni et al., 2006; Meneghetti et al., 2011). A notable difference from the present study is that in these studies participants were asked to recall both landmark identities and their locations. On the other hand, in the present study, participants were given names of to-be-remembered landmarks in the beginning of a test phase. This most likely reduced the burden on their spatial memories, helping senior participants perform competently in the map condition. Nevertheless, in the navigation condition, this advantage did not eliminate the age difference in spatial learning and memory.

Previous studies on age-related changes in spatial learning suggested that among various processes of spatial learning elderly adults have trouble in cognitive mapping in particular, a process with which observers build the mental representation of a configuration of object locations that are experienced separately (e.g., Iaria et al., 2009; Liu et al., 2011). In these studies, participants learned large-scale environments through exploratory navigation in the first-person perspective and subsequently attempted to create layouts of landmarks from an aerial perspective. Consistent with the navigation condition of the present study, senior participants in the previous studies were impaired at this task compared to young participants. By contrast, although the same cognitive mapping process was involved in the map condition of the present study, senior participants reconstructed the layouts as accurately as young participants. This suggests that the integration process itself with which landmark locations are combined into the entire layout remains intact in elderly adults. Instead, impaired performance observed in the previous studies and in the navigation condition likely stemmed from declines in the ability of (1) encoding spatial information from the ground-level perspective, (2) transforming spatial information from ground-level into aerial perspectives, or (3) aligning landmarks learned from multiple orientations with each other, as none of these was necessary in the map condition.

Related to the above, it should be explicitly pointed out that in the present study the memory test was conducted in an aerial perspective that was also used for encoding spatial information in the map condition. As a consequence, participants had to transform spatial information from ground-level to aerial perspectives only in the navigation condition. This transformation was expected to have minimal influence (at least in young participants) because when a similar task was performed by young adults in previous studies, layouts of equivalent accuracy were constructed after learning environments from ground-level and aerial perspectives (Shelton and Gabrieli, 2002; Shelton and McNamara, 2004; Shelton and Pippitt, 2007). However, in the present study, even young participants created more accurate layouts of landmarks in the map condition than in the navigation condition. Although it is not readily clear why there was this discrepancy in findings, the present result does indicate that effects of perspective transformation were not negligible in the navigation condition. This is potentially important for explaining the observed age-related difference in this condition, given that the MTL has been shown to be involved in manipulation of viewpoints in spatial memory (King et al., 2002; Lee et al., 2005); that is, the ability to mentally transform perspectives can decline in aging, possibly causing selective impairment in the navigation condition (Inagaki et al., 2002; Joanisse et al., 2008; Devlin and Wilson, 2010). Thus, in future studies it would be informative to include tasks that do not require transforming perspectives between learning and test in both navigation and map conditions (e.g., a scene recognition task; Shelton and McNamara, 2004). Such tasks would help clarify whether it was types of spatial learning *per se* or mental transformation of spatial information that impacted performance of senior participants in the present study.

Spatial learning through exploratory navigation and spatial learning through map reading are different in a number of respects. The present study focused on two most notable differences between them: perspectives and orientations. Exploratory navigation is carried out in a ground-level perspective with variable orientations, whereas maps are read from an aerial perspective in a stable orientation. In the present study, they were varied simultaneously between navigation and map conditions for achieving naturalistic simulation of exploratory navigation and map reading. Although this approach was effective in revealing the selective effect of aging on spatial learning through exploratory navigation, the present data alone cannot determine whether it originated from viewing environments from the ground-level perspective or learning environmental layouts with varying orientations. Similarly, for the purpose of making strict comparisons between the two conditions, some characteristics of each type of spatial learning were not captured in the present study. For example, one typical advantage of map reading over exploratory navigation is that observers can learn a greater portion of an environment from a single point of view. However, this advantage was not available in the present experiment because approximately the same number of landmarks were made visible at any given time in both conditions in order to avoid a potential confound of general age difference in information processing speed. It is important for future studies to examine possible roles

of these unexplored factors in age-related changes in spatial learning abilities. Such investigations should bring about a clearer understanding of elderly adults' challenges in spatial learning and memory, and eventually a solution for easing their difficulties.

ACKNOWLEDGMENTS

The authors thank Amy Shelton for providing materials used in the experiment, and Albert Smith, Jesse Sargent, and Lucinda Rohde for comments on drafts of this article.

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Conflict of Interest Statement: The authors declare that the research reported in this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 27 March 2012; accepted: 29 May 2012; published online: 12 June 2012.

*Citation: Yamamoto N and DeGirolamo GJ (2012) Differential effects of aging on spatial learning through exploratory navigation and map reading. Front. Ag. Neurosci. **4**:14. doi: 10.3389/fnagi. 2012.00014*

frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 01 June 2012
doi: 10.3389/fnagi.2012.00011

Wading pools, fading memories—place navigation in transgenic mouse models of Alzheimer's disease

Heikki Tanila*

A. I. Virtanen Institute, University of Eastern Finland, Kuopio, Finland

Edited by:
Emma R. Wood, University of Edinburgh, UK

Reviewed by:
Kathy R. Magnusson, Oregon State University, USA
Ashok Kumar, University of Florida, USA

****Correspondence:***
Heikki Tanila, Professor in Molecular Neurobiology, A. I. Virtanen Institute, University of Eastern Finland, P. O. Box 1627, Neulaniementie 2, 70211 Kuopio, Finland.
e-mail: heikki.tanila@uef.fi

The Morris swim navigation task ("water maze") has been a primary research tool to assess hippocampal-dependent spatial learning and memory in rodents for three decades. Originally developed for rats, its application to mouse studies has been a tedious process, but nowadays there are more studies performed with the Morris swim task in mice than in rats. The task has proved to be particularly useful in demonstrating age-related memory impairment in transgenic mouse models of Alzheimer's disease (AD). This review focuses on task details that are most relevant for its application to mouse studies in general and characteristic patterns of impaired performance in Alzheimer model mice as compared with rodents sustaining hippocampal lesions.

Keywords: spatial memory, amyloid-beta, amyloid precursor protein, presenilin-1, tau

INTRODUCTION

Exactly 30 years ago Richard Morris and colleagues published in an article in Nature on a novel behavioral task for place navigation in rats and demonstrated the sensitivity of the task for hippocampal lesions (Morris et al., 1982). Since then the task has been known as the "Morris water maze" and been employed in thousands of published studies worldwide. Originally meant to be a test for rats, which are good swimmers by nature, it also has been successfully applied more and more often to memory testing in mice, which are innately strictly terrestrial animals. To acknowledge the important three decade milestone of this task, this review aims at giving a critical overview of applications of Morris water maze in testing mouse models of the most important memory disorder of mankind, Alzheimer's disease (AD).

IMPORTANT TECHNICAL DETAILS IN THE TASK

In fact, the name "water maze" is a misnomer in the strictest meaning of the word, because the task is performed in an open wading pool and not in a labyrinth-like series of pathways. In particular, since one of the earliest modifications of the swim task was to place a walled radial maze inside the wading pool, resulting in a true water maze [usually called a "radial-arm water maze"; (Buresová et al., 1985)], it would be more appropriate to call the original task the "Morris swim navigation task" or simply as the "Morris swim task," as will be done in this review. The test environment consists of a wading pool with a diameter of 120–200 cm and a movable submerged platform, which can vary from 10 to 15 cm in diameter, based on animal size. The submerged platform has to be placed close enough to the surface so that a swimming animal will not be able to swim over it without noticing the platform. Several tricks have been used to make sure that the platform really is hidden from the animal. The original trick was to use milk powder to make the water opaque. Because of the bacterial growth this is not an ideal solution, and has been replaced by inorganic white pigment. Another strategy is to avoid any additives in the water by making both the pool and the platform of matt black plastic and provide the room lighting so that light reflects from the water surface. This approach gives a beautiful contrast for video tracking with a white albino rat, but is much less optimal for the most common mouse strain used in place navigation studies, the C57BL/6 mouse. Having marked black mice with a piece of white adhesive tape for years, our lab eventually decided to use a pool made of white plastic and a transparent plastic platform, which combination eventually proved to work. Even though numerous published studies have only utilized a stopwatch to measure the escape latency as a measure of learning in the Morris swim task, this is not acceptable, because of the lack of control for the swimming speed. A good-quality video tracking system is a must for a proper task monitoring. Besides providing a measure of the swim path length for speed calculation, it also yields several other parameters that help identify the strategy and nature of memory impairment of the animal, such as the mean distance from the wall or from the platform, and occupancy near the platform location in the probe trial without the presence of the platform itself.

The standard swim navigation task consists of 3–8 acquisition trials for 3–5 days, with the platform kept in a fixed location. The last trial of the last day is usually a probe trial, without the platform, to see the eventual search bias of the animal. Ideally, the animal would swim in small circles tightly around the former platform location to indicate that it has an established memory of the location. The probe trial can be delayed to or replicated on the next day to reveal more long-term retention of the memory for the specific location. Some details in the task design are fundamentally important for the desired specificity for hippocampal function. First, the starting positions have to vary to make the

task performance dependent on true navigation and not egocentric response learning. If a constant start position is used, the task performance will no longer be impaired by hippocampal lesion (Eichenbaum et al., 1990). Second, the environment must provide multiple prominent cues for triangulation. On the other hand, a single cue may not be too prominent, because it will easily attract the animal as a beacon. Especially for mice, this prominent cue is the experimenter him- or herself! A not uncommon error for the experimenter is to anticipate picking up the animal and moving toward the platform at the end of the trial, thus providing a strong cue leading to the target. Besides the probe trial for search bias, the original task design also included another control trial, a visible platform variant of the task. Normal performance in this version, with the platform above the water surface or marked with a pole and flag, should imply that the animal is motivated to climb onto the platform, able to master the motor task requirements, and has normal vision. However, with respect to exclusion of visual impairment, the ability to use the visual platform task as a control has been questioned (Lindner et al., 1997). Rats with hippocampal lesions show initial impairment also in the visual platform task (Morris et al., 1982). So the true value of adding this version is somewhat in doubt. More importantly, it makes a big difference whether visual platform task is run before or after the hidden platform task. If run before in the usual way with curtains around the pool to eliminate all distal cues, it encourages the animal to ignore the distal landmarks, which in the next phase become fundamentally important. This task protocol may thus discourage the use of true navigation strategy and favor the development of alternate search strategies, which eventually show up as poor performance in the probe task. Therefore, it would be recommended to run the visible platform task after the hidden platform version or skip that altogether.

THE TASK IS APPLICABLE TO MICE AFTER ALL

Initial experiences in applying the Morris swim navigation task to mice were so discouraging that it was long speculated that mice, as strictly terrestrial animals, are not capable of learning the task at all. For instance, one hallmark study that directly compared place learning between C57Bl/6 mice and Long–Evans rats showed mice to be inferior learners in the Morris swim task, even though their performance was equal to rats on a dry radial-arm maze (Whishaw and Tomie, 1996). The authors attributed the inferior performance of mice in the swim task to the better adaptation of rats to swimming. However, there are a number of less well known factors that may account for the poor performance of mice in the Morris swim task even to a greater extent than the simple motor aspect of swimming.

The first important difference in cognitive abilities between mice and rats are robust differences between mouse strains in their learning ability (see Kennard and Woodruff-Pak, 2011 for a recent review). This is a general problem in using mice in cognitive tasks, but especially pronounced in the Morris swim task, because there are strain differences not only in spatial memory *per se*, but also in visual acuity and the learning pattern (Kennard and Woodruff-Pak, 2011). In fact, one reason why the C57BL/6, among all laboratory mouse strains, has become the most widely used strain in cognitive testing derives from its good performance in place learning tasks, including the Morris swim task (Owen et al., 1997). This mouse strain is also suitable for aging studies, showing impairment in spatial memory between 12 and 24 months of age according to various studies. In contrast, FVB, 129/Sv, and DBA strains, which are often found in genetically engineered hybrid lines, are clearly inferior in spatial learning as measured in the Morris swim task (Kennard and Woodruff-Pak, 2011).

One severe problem with mice, as compared to rats, is that many mice actually avoid the escape platform. If they find it accidentally, they may jump off and continue swimming. This may be partly related to the common habit of picking up mice with a net, which they experience as highly aversive. Furthermore, as worse swimmers than rats, mice occasionally have difficulties in climbing onto the platform. An established solution in mouse pool testing is to give them an extra day of pretraining in an alley that leads to the platform. A second and still largely unsolved problem is that mice often do not display a clear search bias in the probe task. One obvious problem in early studies was the downscaling of the pool size in order to correspond to the difference in body sizes between the rat and the mouse. The use of a pool with a diameter as small as 80–90 cm resulted in mice swimming in large circles, but maintaining the appropriate distance from the pool wall. Enlarging the pool to almost the same size as used for rats seemed to solve the problem, but only partially. The fundamental problem seems to be that the mice do not develop the habit of swimming in small circles around the presumed platform location in the probe trials like the rats do. Rather, they make a quick search of the presumed location of the platform, and as soon as they fail to find it, they return to the start location or begin to swim toward the experimenter in the hope of getting picked up (**Figure 1**). Therefore, the most commonly used occupancy-based parameters for assessing spatial memory, such as "time in the target quadrant" or "time in the vicinity of the platform," do not reveal as clear a search bias as corresponding parameters in rats. A recent systematic study comparing the power of various parameters to assess search bias in mice came to the conclusion that the best parameter to assess spatial memory in the Morris swim task is

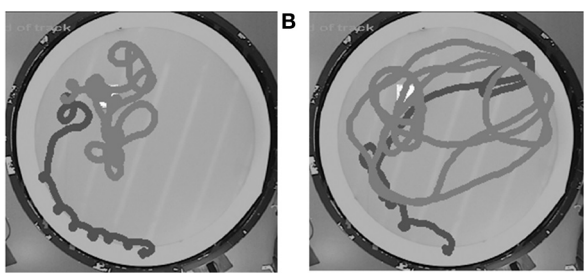

FIGURE 1 | It is unusual for mice to demonstrate the ideal search pattern in the probe test (A). Instead, they usually make one approach to the correct former platform position. As soon as they fail to find the platform, they switch to a wider search pattern, but still show some preference to the original target area **(B)**. Black trace: first 20 s, gray trace: following 40 s. The white square indicates the original platform location. Pool diameter 120 cm.

the mean distance to the former platform location (Maei et al., 2009).

Finally, the small body size and especially the thin layer of subcutaneous fat, as compared to rats, render mice susceptible to hypothermia during prolonged exposure to the pool water, which is kept close to room temperature for practical reasons and to ensure sufficient motivation to escape from the water. In the first systematic study on this topic, we found to our great surprise that the regular five daily swims in 20°C water with 30 s between the trials was enough to cause up to 9°C drop in the rectal temperature (Iivonen et al., 2003). The decline in core temperature was accompanied by slowing of the swimming speed. Moreover, the effect was dependent on the sex and genotype of the mice; females were more susceptible to hypothermia than males and transgenic mice carrying Alzheimer-associated APP and PS1 mutations were more vulnerable than their non-transgenic littermates, because of a smaller body weight. Raising the water temperature from 20 to 24°C only partially alleviated the hypothermia. However, increasing the inter-trial interval from 30 s to 13 min removed the net cooling effect of five trials on the core temperature and swimming speed. It is nowadays a common practice to allow mice enough time to warm up between the swims and to assist with external heating devices. Nonetheless, vulnerability to hypothermia is a serious limitation in experimental planning. For instance, in the context of aging studies, a long line of evidence suggests that training distributed over several days is less sensitive to age-related place learning impairment than massed trials (see Foster, 2012 for review). One quite common procedure with aged rats is to give eight trials on one day followed by a probe test 24 h later. This would be very difficult to adapt to mice, which on the one hand would require more trials than rats to attain the same spatial bias and on the other hand would not tolerate the unavoidable hypothermia induced by such massive water exposure.

MORRIS SWIM TASK HAS BECOME A GOLD STANDARD TEST FOR MEMORY IN AD MOUSE MODELS

Notwithstanding all the above mentioned precautions, the Morris swim navigation task has become the gold standard in demonstrating spatial memory impairment in mouse models of AD. In contrast to large differences between various transgenic AD model mice in several common memory tests, such as fear conditioning or object recognition, all established AD model mice show deficits in the Morris swim task as they age. In addition, the impairment is highly reproducible. We have tested about 3000 APP/PS1 transgenic mice in the Morris swim task during the past 10 years, and have never failed to see an impairment in a test group of transgenic mice, as compared to their wild-type littermates, provided that the mice were past a critical age. Using the terminology for assessing animal models of human disease, one can say that the Morris swim navigation task has *face validity*, because one of the most prominent everyday problems of AD patients is easily getting lost outside their home environment. The test can be considered to have *construct validity*, since transgenic mouse models of AD, whether carrying single APP mutation, combined APP + PS1 mutation, or tau mutation, all display age-related impairment in the task performance (**Table 1**). Finally, the task has *predictive validity*, because all AD drugs in clinical use at present (rivastigmine, galantamine, donepezil, memantine) show a beneficial effect in the Morris swim task in various mouse models (Sweeney et al., 1988; Minkeviciene et al., 2004; Van Dam et al., 2005, 2008).

DIFFERENT NATURE OF IMPAIRED TASK PERFORMANCE BETWEEN AD MODEL MICE AND RODENTS WITH HIPPOCAMPAL LESIONS

There are some important differences in the spatial learning deficit in the Morris swim task between transgenic AD model

Table 1 | Summary of genetic mouse models of Alzheimer's disease with reported impairment in the Morris swim navigation task.

Transgene	Mouse line	Onset age (months)	References
APP			
huAPP751	APP751	<12	Moran et al., 1995
APP-CTF	APPC100	10	Berger-Sweeney et al., 1999
APPswe	APP23	3	Van Dam et al., 2003
APPswe	Tg2576	6	Westerman et al., 2002
APPswe,ind	TgCRND8	3	Chishti et al., 2001
APPind	PDAPP	<13	Daumas et al., 2008
APPswe,ind	J20	6–7	Palop et al., 2003
APP + PS1			
APPswe/PS1 (M146L)	APP/PS1 (M146L)	6–8	Trinchese et al., 2004
APPswe/PS1(A246E)	APP/PS1(A246E)	11–12	Puoliväli et al., 2002
APPswe/PS1dE9	APdE9	10–14	Minkeviciene et al., 2008
APP + PS1 + tau			
APPswe/PS1(M146V)/tauP301L	3xTg-AD	4	Billings et al., 2005
Tau			
P301L tau	Tg4510	1.3	Santacruz et al., 2005
G272V and P301S tau	THY-Tau22	3–10	Schindowski et al., 2006

The onset age for the impairment is indicated.

mice (at least in APP transgenics that have been studied the most) and rodents with hippocampal lesions. First, the learning deficit in transgenic mice is never as severe as in animals with hippocampal lesions, and the transgenic mice are usually able to learn the task if allowed some extra training. In this regard, APP transgenic mice closely resemble aged rats (Foster, 2012). Notably, these statements are largely based on comparison between published studies, since few studies have compared the outcome of an experimental lesion with the pathological changes induced by a genetic manipulation. One demonstrative example is our study from 10 years ago, in which we compared the effects of the APP/PS1 transgenic background and fimbria-fornix transection (FFX) on spatial learning in the Morris swim task in C57BL/6 mice (Liu et al., 2002). While the FFX mice showed practically no improvement during five days, APP/PS1 mice showed a clear learning curve, albeit a slower task acquisition than wild-type littermates. A second difference between transgenic APP mice and animals with hippocampal lesions is in the number of cognitive processes affected. When we compared learning within and between daily sessions, a clear dissociation emerged between APP/PS1 and FFX mice. Whereas FFX mice were impaired in both within and between session learning, APP/PS1 mice showed robust learning within a session, but seemed to forget most of what they learned by the next morning (Liu et al., 2002). This "saw-tooth" learning curve in the Morris swim task is also a common finding in aged rats (Foster, 2012). A parsimonious explanation of this difference is that the hippocampus is necessary for navigation (triangulation based on external landmarks and self-motion) in real time, as well as for episodic encoding and memory consolidation. In contrast, accumulation of amyloid-β in the hippocampus interferes only with the long-term memory formation. The susceptibility of APP transgenic mice for faster forgetting of spatial information has been confirmed in at least two other mouse models in later studies (Billings et al., 2005; Daumas et al., 2008). The third difference is that long escape latencies at an early stage of task acquisition in APP transgenic mice are largely due to strong thigmotaxis, which is a prominent feature in genetically modified mice in the Morris swim task in general (Lipp and Wolfer, 1998). This is illustrated in **Figure 2**, which shows parallel learning curves for 12-month-old APdE9 and wild-type littermate male mice in terms of escape latency (**Figure 2A**), path length (**Figure 2B**), and time spent in the wall zone (**Figure 2C**). On top of strong thigmotaxis, APdE9 mice also show poor search bias in the probe test (**Figure 2D**). Without any doubt the Morris swim task is a complex one and involves many cognitive processes at the same time, such as general adaptation to the stressful situation, abandoning of an ineffective tendency to search for an escape in the pool wall, locating the submerged platform based on distal landmarks, and finally encoding that information to long-term memory. A human analogy may be to give the task of delivering a package by bike to a remotely known address in a city to a person who has never ridden a bike before. The learning process involves the motor aspect of bike riding, learning how to cope with busy traffic, and finally, by

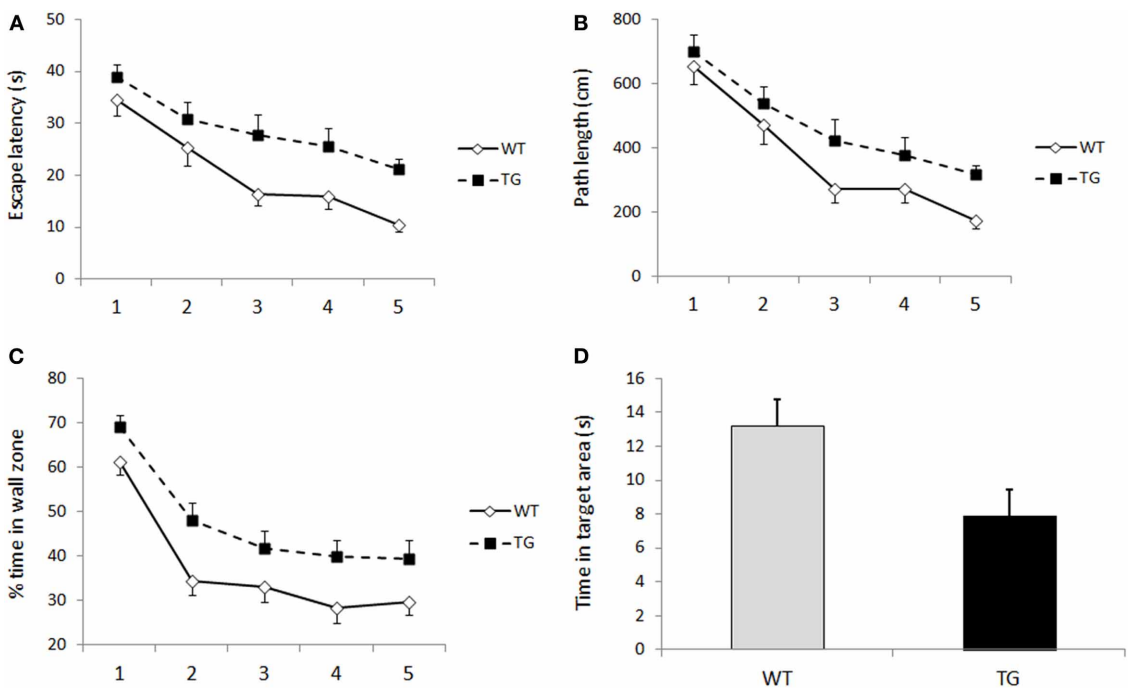

FIGURE 2 | (A) Escape latency over five days of Morris swim task acquisition in 12-month-old male APPSwe/PS1dE9 (tg, $n = 13$) mice and their wild-type littermates (WT, $n = 15$). Genotype difference was significant ($p = 0.001$, ANOVA with repeated measures). Group means and SEMs are shown. **(B)** Corresponding plot for path length ($p = 0.01$, ANOVA with repeated measures). **(C)** Thigmotaxis, in terms of % time in the most peripheral 1/3 of the pool area, showed a similar time course as escape latency and path length ($p = 0.001$, ANOVA with repeated measures). **(D)** The genotypes also differ in the time spent in the former platform area (diameter 30 cm) during the probe test on the last trial of day 5 ($p = 0.03$, Student's *t*-test).

trial and error, to remember successful and unsuccessful routes to the destination in a complex city map. In fact, it may be the feature of the Morris swim task to draw on several parallel cognitive processes that explains its sensitivity to demonstrating cognitive impairment in AD model mice. It is likely that several cognitive processes are compromised in APP transgenic mice due to synaptic pathology involving both the hippocampus and neocortex.

WHICH BRAIN PATHOLOGY ACCOUNTS FOR THE SPATIAL LEARNING IMPAIRMENT IN AD MICE?

What then is the pathological feature in AD model mice which accounts for the impaired task acquisition and development of search bias in the Morris swim task? An important feature of all established APP transgenic mouse models is that very young mice (∼2 months) are indistinguishable from their wild-type littermates in the task performance. Because the APP transgene is translated to protein already during a late embryonic stage, normal performance in young transgenic mice implies that the behavioral deficit is not due to a developmental abnormality, but rather to age-related neurodegeneration. The same conclusion can be drawn from conditional mutant tau expressing mice (Santacruz et al., 2005). An obvious candidate accounting for the behavioral deficit is amyloid plaque formation. However, the available literature does not support a direct relationship between amyloid plaque formation and spatial memory deficit. Namely, the time course between amyloid plaque formation and the onset of spatial memory deficit varies greatly between different APP transgenic mouse lines. As exemplified in **Figure 3**, some mouse lines show memory impairment before the first amyloid plaques can be found in a neuropathological examination, while in some other mouse lines these two events can co-occur, and in some other lines, memory impairment may follow amyloid plaque formation by several months.

The poor correlation between amyloid plaque load in postmortem examination and performance in cognitive tests is also a well-established finding in human studies (Nagy et al., 1995).

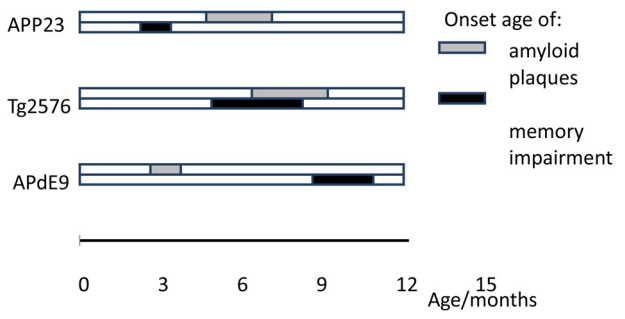

FIGURE 3 | Timeline of amyloid plaque deposition vs. memory impairment in the Morris swim task in three different APP transgenic mouse lines: APP23 (APPswe under Thy-1 promoter, Van Dam et al., 2003), Tg2576 (APPswe under hamster PrP promoter, Kawarabayashi et al., 2001; Westerman et al., 2002), and APdE9 (APPswe and deletion of exon 9 of presenilin-1 under mouse PrP, Garcia-Alloza et al., 2006; Minkeviciene et al., 2008).

However, it is possible that these different mouse lines exhibit different harmful effects induced by Aβ formation. For instance, memory deficits before plaque formation may model the impact of soluble Aβ oligomeric species, whereas memory deficits after plaque formation may model the impact of inflammatory mediators around the plaques. An issue that has attracted little attention so far is whether the exact nature of impaired performance in such a complex task as Morris swim navigation also differs between those mouse lines that show early vs. late memory impairment with regard to the appearance of amyloid plaques. Similarly, the correlation between insoluble intracellular tau deposits and impaired Morris swim task performance is not straightforward. Turning off the inducible P301L tau mutant transgene restores the task performance, but if done at a later time point than tau aggregation begins, tau aggregates continue to accumulate in the brain (Santacruz et al., 2005). This finding implies that also for tau aggregates, the soluble species may be the most harmful ones for memory formation.

POTENTIAL AND LIMITATIONS OF THE MORRIS SWIM TASK IN EXPERIMENTAL AD RESEARCH

As with any test, the Morris swim task has its limitations. It is often criticized for being too stressful for the animals (Kennard and Woodruff-Pak, 2011). This is unavoidable, but the stress level can be reduced by proper pretraining and the use of testing schemes that allow sufficient time for mice to recover between trials. The concern about stressfulness, however, is outweighed by the guaranteed motivation for mice to perform a cognitive task for several days in a row without strict food restriction, which by itself may interfere with the disease process. Another serious limitation is that the classic version of the task is basically a once-a-lifetime learning experience. We have tried to test the same APdE9 mice at a young age before AD pathology and a second time around 12 months of age. Despite several intervening months, the mice show very rapid initial task learning. On the other hand, repeated testing has been successfully applied when mice are trained to criterion using one platform position and then introduced to a new task with a novel platform position repeatedly (Chen et al., 2000). However, this approach is quite tedious and is not well-suited for testing a large number of mice at two different age points. For this purpose, the radial-arm water maze may be a more appropriate solution (Alamed et al., 2006). Nevertheless, because of its established role as the gold standard memory test and the accumulated reference material over the years, the classic Morris swim navigation task is likely to prevail for years as a central tool in the cognitive assessment of AD model mice, both in studies delving into the disease pathogenesis and studies on the efficacy of new therapeutic interventions. Therefore, knowledge about its use potential and pitfalls should be available in all laboratories working on cognitive assessment of AD model mice.

ACKNOWLEDGMENTS

Supported by EU 7th Framework program grant HEALTH-F2-2007-201159. I wish to thank Susanna Kemppainen for technical assistance in the manuscript preparation.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 22 March 2012; paper pending published: 16 April 2012; accepted: 15 May 2012; published online: 01 June 2012.

Citation: Tanila H (2012) Wading pools, fading memories—place navigation in transgenic mouse models of Alzheimer's disease. Front. Ag. Neurosci. ***4****:11. doi: 10.3389/fnagi.2012.00011*

frontiers in
AGING NEUROSCIENCE

MINI REVIEW ARTICLE
published: 29 May 2012
doi: 10.3389/fnagi.2012.00009

Less efficient pattern separation may contribute to age-related spatial memory deficits

Heather M. Holden [1] ***and Paul E. Gilbert*** [1,2]*

[1] *Department of Psychology, San Diego State University, San Diego, CA, USA*
[2] *San Diego State University, University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA*

Edited by:
Emma R. Wood, University of Edinburgh, UK

Reviewed by:
Junming Wang, University of Mississippi Medical Center, USA
Ashok Kumar, University of Florida, USA

***Correspondence:**
Paul E. Gilbert, San Diego State University, University of California San Diego Joint Doctoral Program in Clinical Psychology, 6363 Alvarado Court, Suite 103, San Diego, CA 92120, USA.
e-mail: pgilbert@sciences.sdsu.edu

Spatial memory deficits have been well-documented in older adults and may serve as an early indicator of mild cognitive impairment (MCI) or Alzheimer's disease (AD) in some individuals. Pattern separation is a critical mechanism for reducing potential interference among similar memory representations to enhance memory accuracy. A small but growing literature indicates that spatial pattern separation may become less efficient as a result of normal aging, possibly due to age-related changes in subregions of the hippocampus. This decreased efficiency in spatial pattern separation may be a critical processing deficit that could be a contributing factor to spatial memory deficits and episodic memory impairment associated with aging. The present paper will review recently published studies in humans, non-human primates, and rodents that have examined age-related changes in spatial pattern separation. The potential basic science, translational, and clinical implications from these studies are discussed to illustrate the need for future research to further examine the relationship between spatial pattern separation and brain changes associated with aging and neurodegenerative disease.

Keywords: hippocampus, dentate gyrus, aging, spatial memory, interference, pattern separation

SPATIAL MEMORY DECLINE IN AGING

In the United States, Alzheimer's disease (AD) is the most common cause of dementia in older adults and accounts for 60–80% of dementia cases (Alzheimer's Association, 2012). In the year 2012, an estimated 5.4 million Americans will be diagnosed with AD, however, this number is projected to increase to 11–16 million by 2050 (Alzheimer's Association, 2012). As a result of the aging "baby boom" generation and increasing longevity in the US population, the disease is a growing public health concern with costs estimated to reach $200 billion in 2012. Although a number of risk factors for AD have been discussed (e.g., diagnosis of mild cognitive impairment (MCI), family history of AD, apolipoprotein epsilon E4 allele), one of the most well-documented risk factors for the disease is increasing age (Kamboh, 2004). Therefore, a major aim of recent research has focused on identifying early indicators of cognitive dysfunction in older adults.

A variety of cognitive functions may be affected in older adults, however, one of the most commonly reported deficits associated with aging is memory loss. Although not all memory domains are equally affected by aging (e.g., source vs. item memory), some domains such as spatial memory appear to be particularly sensitive to age-related change. Age-related spatial memory decline has been well-documented in both humans (reviewed by Iachini et al., 2009) and animal models (reviewed by Sharma et al., 2010). Spatial memory deficits also have been well-documented in older adults diagnosed with AD (Sahakian et al., 1988; Kessels et al., 2005) or mild cognitive impairment (MCI: Alescio-Lautier et al., 2007; deIpolyi et al., 2007; Hort et al., 2007). Some evidence suggests that spatial memory deficits even may serve as an early indicator of AD (Buccione et al., 2007; deIpolyi et al., 2007; Hort et al., 2007). Age-related spatial memory deficits may result from changes in a variety of brain regions including the hippocampus, temporal lobes, and the frontal-parietal network (Iachini et al., 2009). In particular, spatial memory decline associated with aging has been suggested to result from age-related changes in the hippocampus across species (reviewed by Barnes, 1988). However, it is only recently that studies have begun to examine how age-related changes in particular subregions of the hippocampus may affect specific mnemonic processes. One such process is spatial pattern separation, a mechanism that may be essential for the accurate formation and retrieval of spatial memories. Less efficient spatial pattern separation in older humans and animals may contribute to impairments in spatial memory, particularly in situations when spatial interference is high.

PATTERN SEPARATION

Pattern separation is a mechanism for separating partially overlapping patterns of activation so that one pattern may be retrieved as separate from other similar patterns. A pattern separation mechanism may be critical for reducing potential interference among similar memory representations to enhance memory accuracy (Gilbert and Brushfield, 2009). A number of models have suggested that the hippocampus supports pattern separation (Marr, 1971; McNaughton and Nadel, 1990; O'Reilly and McClelland, 1994; Shapiro and Olton, 1994; Rolls and Kesner, 2006; Kesner, 2007; Myers and Scharfman, 2009; Rolls, 2010). In particular, the dentate gyrus (DG) and CA3 subregions of the hippocampus have been shown to play a critical role in

pattern separation in animal models using electrophysiological methods (McNaughton et al., 1989; Tanila, 1999; Leutgeb et al., 2007), neurotoxin-induced lesions (Gilbert et al., 2001; Lee et al., 2005; Gilbert and Kesner, 2006; Goodrich-Hunsaker et al., 2008; McTighe et al., 2009; Morris et al., 2012), and genetic manipulations (Kubik et al., 2007; McHugh et al., 2007). In addition, studies using high-resolution functional magnetic resonance imaging (fMRI) have shown that the human hippocampus (Kirwan and Stark, 2007), and specifically the DG/CA3 subregions (Bakker et al., 2008; Lacy et al., 2011), are active during pattern separation tasks (also see reviews by Carr et al., 2010; Yassa and Stark, 2011b).

AGE-RELATED CHANGES IN THE BRAIN

Aging has been shown to result in gray matter and white matter changes in a variety of brain regions (Allen et al., 2005; Ziegler et al., 2008; Driscoll et al., 2009; Kennedy and Raz, 2009), including the hippocampus (Good et al., 2001; Allen et al., 2005; Driscoll and Sutherland, 2005; Raz et al., 2005; Walhovd et al., 2010). Longitudinal studies have reported that non-demented older adults show decreased volume in the hippocampus and parahippocampal cortices (Driscoll et al., 2009). However, hippocampal volume has been reported to decrease at a faster rate than other medial temporal lobe structures (Raz et al., 2004). Longitudinal changes in hippocampal volume have been shown to be the primary determinant of memory decline (Mungas et al., 2005; Kramer et al., 2007). fMRI signal intensity has been shown to decline in all hippocampal subregions in older adults (Small et al., 2002). However, the DG subregion may be particularly susceptible to age-related changes in both humans (Small et al., 2002) and animal models (Small et al., 2004; Patrylo and Williamson, 2007). In addition, significant age-related changes have been documented in the perforant pathway in both humans (Yassa et al., 2011a) and animal models (Geinisman et al., 1992). This diminished input from the entorhinal cortex to the DG also may impact connections to the CA3 subregion and this reduction in connectivity was shown to reliably predict spatial learning deficits in old rats (Smith et al., 2000).

PATTERN SEPARATION AND AGING

There is a small but growing literature suggesting that pattern separation may be adversely affected by aging. Wilson et al. (2006) proposed a model to account for age-related susceptibility to interference. This model suggests that age-related changes in the DG subregion of the hippocampus may result in less efficient pattern separation due to an impaired ability to reduce similarity among new input patterns. Furthermore, age-related changes in the hippocampus strengthen the autoassociative network of the CA3 subregion that supports pattern completion, a mechanism that allows a complete representation of stored information to be retrieved using partial cues. These age-related changes may cause the CA3 subregion of the hippocampus to become entrenched in pattern completion at the expense of processing new information and pattern separation. As further evidence for this hypothesis, a recent study by Yassa et al. (2011a) reported that reduced pattern separation activity in the DG/CA3 regions of aged humans was linked to structural changes in the perforant pathway. The changes were suggested to weaken the processing of novel information while strengthening the processing of stored information. Shing et al. (2011) report that increased false alarm rates in older adults when performing an episodic memory task may be linked to CA3–4/DG volume, which may reflect individual age-related differences in maintaining a pattern separation-pattern completion equilibrium.

Given the well-documented role of the DG in supporting pattern separation and the potential susceptibility of this region to age-related change, recent behavioral studies have begun to examine pattern separation in older humans. Using a continuous recognition paradigm developed by Kirwan and Stark (2007), Toner et al. (2009) reported that non-demented older adults are impaired on a pattern separation task for visual object information. A subsequent fMRI study supported these findings and additionally demonstrated increased age-related activity in the DG and CA3 subregions when pattern separation demands were high on a visual object task (Yassa et al., 2010a).

SPATIAL PATTERN SEPARATION IN OLDER HUMANS

Recent studies also have begun to examine spatial pattern separation deficits in older adults. A study by Stark et al. (2010) reported that spatial pattern separation is impaired in a subset of older adults. Participants studied unique pairs of pictures and later were asked to identify whether the pictures were both in the same location as before or whether one of the pictures was in a different location. In the *same* condition, neither of the pictures in a pair was moved. In the three *different* conditions (close, medium, far) the location of one of the pictures in a pair was moved by varying both the distance and the angle from the original location. Older adults were separated into an *aged impaired* group and *aged unimpaired* group, based on standardized word learning task performance. Analyses revealed performance deficits on the *close, medium,* and *far* trials for the *aged impaired* group relative to both the *aged unimpaired* and young groups. Therefore, the findings suggest that spatial pattern separation may be impaired in a subset of older adults.

A subsequent study by Holden et al. (2012) examined the ability of cognitively normal young and older adults to perform a spatial memory task involving varying degrees of spatial interference to assess spatial pattern separation. During the sample phase of each trial, a circle appeared briefly on a computer screen. The participant was instructed to remember the location of the circle. During the choice phase, two circles were displayed simultaneously and the participant was asked to indicate which circle was in the same location as the sample phase circle. The two choice phase circles were separated by one of four possible spatial separations across trials: 0, 0.5, 1.0, and 1.5 cm. Smaller separations are likely to create increased overlap among memory representations, which may result in heightened interference and a greater need for pattern separation. Consistent with this hypothesis, the performance of both young and older adults increased as a function of increased spatial separation. However, young adults outperformed older adults, suggesting that spatial pattern separation may be less efficient in older adults. In an attempt to replicate the findings of Stark et al. (2010), the older adult group was separated into *older impaired* and *older unimpaired* groups based

on performance on a standardized delayed word recall measure. Consistent with Stark et al. (2010), the *older impaired* group was significantly impaired relative to both the *older unimpaired* and young groups.

SPATIAL PATTERN SEPARATION IN OLDER ANIMALS

Kubo-Kawai and Kawai (2007) conducted a study in aged monkeys that is similar in nature to the two aforementioned studies conducted in older humans. This study tested young and older monkeys on a delay non-match-to-position task involving manipulations of the spatial distance between two locations. During the sample phase, a plate was positioned to cover a baited food well along a single row of four food wells. The animal displaced the plate to receive a reward. During the choice phase, an identical plate was positioned to cover the unbaited sample phase well (incorrect choice) and a second identical plate was positioned to cover a different baited food well in one of the three remaining locations (correct choice). The distance between the two choice phase plates was manipulated across trials and included separations of 12, 24, and 36 cm. The data showed that the ability of both young and older monkeys to choose the correct plate improved as a function of increased spatial separation between the two plates during the choice phase. However, no age-related differences in performance were detected across separations. In a second experiment, the sample phase followed the same procedure described for the previous experiment. However, on the choice phase, two rows of food wells were used. The plate covering the unbaited sample phase food well (incorrect choice) was located on one row, whereas the plate covering the new location was positioned to cover a baited food well (correct choice) on a different row of wells. Spatial separations of 15, 25.6, and 37.1 cm were used to separate the plates across choice phase trials. The data revealed that older monkeys were impaired relative to young monkeys across all three separations, with the largest group differences found on trials involving the closest 15 cm separation. One could speculate that smaller separations were likely to create increased overlap among memory representations, which may result in heightened interference and a greater need for pattern separation. Although this study was not designed or interpreted by the authors to assess pattern separation, these findings in aged monkeys are in accordance with the findings from the studies involving older humans.

A recent study from our lab (Gracian et al., unpublished observations) provides further behavioral evidence that spatial pattern separation may be impaired in aged animals. Young and old rats were trained on a radial eight-arm maze to discriminate between a rewarded arm and a non-rewarded arm that were either adjacent to one another (high spatial interference) or separated by a distance of two arm positions (low spatial interference). Performance on this task recently was shown to be dependent on the DG hippocampal subregion (Morris et al., 2012). Gracian et al. showed that young and old rats committed similar numbers of errors in the separated condition. However, in the adjacent condition, old rats committed significantly more errors compared to young rats. The results suggest that decreased spatial pattern separation in aged rats may impair performance on the adjacent condition, which involved greater spatial interference among distal cues. However, performance increased in the separated condition when there was less overlap among distal cues and less need for pattern separation.

A recently published study by Marrone et al. (2011) provides further neurobiological insight into how age-related changes in the DG may affect pattern separation and spatial memory. In this study, young and aged rats were allowed to explore either: (1) the same environment on two occasions or (2) one environment followed by a different environment. A marker of cellular activity (zif268/egr1) was used to examine granule cell activity during exploration of the environments. Older animals were found to recruit distinct populations of granule cells during exploration of the same environment on two different occasions, which the authors interpret to be an indication of greater pattern separation. However, when the aged animals visited different environments, the reliability of repeated zif268 expression in young and aged animals was comparable, thus the age-related increase in pattern separation was no longer apparent. The study also found that increased pattern separation in the similar contexts was correlated with a reduced ability of older animals to disambiguate similar contexts during a sequential spatial recognition task. The authors conclude that spatial memory performance in aged animals is most impaired in situations where interference is increased, presumably due to decreased pattern separation. Collectively, the aforementioned studies offer evidence that spatial pattern separation may become less efficient as a result of aging.

IMPLICATIONS

Age-related memory decline has been suggested to stem from subregion-specific epigenetic and transcriptional changes in the hippocampus (Penner et al., 2010). For example, neurogenesis is reduced in aged animals (Kuhn et al., 1996) and is related to decreased hippocampal volume and impaired performance on hippocampal-dependent tasks (Driscoll et al., 2006). These newborn neurons may be involved in mnemonic processes particularly dependent on the DG subregion, such as pattern separation (Clelland et al., 2009; Aimone et al., 2010, 2011; Creer et al., 2010; Deng et al., 2010; Sahay et al., 2011), whereas older DG cells may contribute to pattern completion (Nakashiba et al., 2012). Sahay et al. (2011) suggest that interventions that increase neurogenesis during adulthood may have clinical implications for reversing age-related impairments in pattern separation and associated DG dysfunction. Therefore, the development of behavioral tasks sensitive to age-related changes in spatial pattern separation may have implications for future studies of neurogenesis.

Age-related changes in spatial pattern separation also may contribute to episodic memory deficits, which have been well-documented in older adults (Rand-Giovannetti et al., 2006) and are a prominent feature of AD that may be detectable several years before disease onset (Bondi et al., 1999). Episodic memory also is impaired in non-demented older adults who are at risk for AD based on genetics (Saunders et al., 1993) or a diagnosis of MCI (Hodges et al., 2006). One key feature of episodic memory that differentiates it from other types of memory is that the elements of an episodic memory must be associated into a context to demarcate the episode in space and time. In addition, a pattern separation mechanism may be necessary to separate

the elements of different episodic memories to avoid interference (Gilbert et al., 2001). It is possible that less efficient spatial pattern separation in older adults may result in poorer memory due to increased interference among the spatial components of episodic memories. The identification of a key mnemonic processing deficit in pattern separation may result in behavioral interventions that structure daily living tasks to mitigate interference in the spatial domain and potentially improve spatial and episodic memory in older adults.

Normal and pathological aging may have differential effects on hippocampal subregions. The DG subregion may be particularly susceptible to age-related changes in humans, however, there may be less impact on pyramidal cells in the CA subregions (Small et al., 2002). In contrast, the CA subregions may be more vulnerable to pathological changes associated with AD (Braak and Braak, 1996; West et al., 2000; Price et al., 2001; Apostolova et al., 2010). As mentioned previously, a primary goal in AD research is to identify risk factors and preclinical markers of the disease in older adults. Given the differential effects of normal aging and AD on the various subregions of the hippocampus, tasks that are sensitive to dysfunction in particular subregions, such as measures of pattern separation, may help to differentiate between cognitive impairment associated with normal aging and pathological changes associated with AD. In support of this idea, a recent study by Yassa et al. (2010b) reported that individuals with amnestic MCI show impairments compared to healthy older adults on an object recognition memory task that taxes pattern separation. In addition, structural and functional changes were observed in the DG/CA3 hippocampal subregions of these individuals.

CONCLUSIONS

In conclusion, spatial memory deficits have been well-documented in older adults and may serve as an early indicator of MCI or AD in some individuals. The operation of a pattern separation mechanism may be critical for reducing interference among similar memory representations to enhance memory accuracy. Evidence suggests that brain regions critical to pattern separation, including the DG and CA3 hippocampal subregions, may be particularly susceptible to adverse age-related changes. A small but growing literature indicates that spatial pattern separation may become less efficient as a result of normal aging. This decreased efficiency in pattern separation may contribute to spatial memory deficits and episodic memory impairment associated with aging. Based on the aforementioned studies, it is clear that additional research is needed to examine the relationship between spatial pattern separation and brain changes associated with aging and neurodegenerative disease.

ACKNOWLEDGMENTS

A portion of the research reviewed in the paper was supported by a National Institutes of Health Grant (#AG034202) from the National Institute on Aging awarded to Paul E. Gilbert.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 29 March 2012; paper pending published: 27 April 2012; accepted: 14 May 2012; published online: 29 May 2012.

*Citation: Holden HM and Gilbert PE (2012) Less efficient pattern separation may contribute to age-related spatial memory deficits. Front. Ag. Neurosci. **4**:9. doi: 10.3389/fnagi.2012.00009*

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 21 May 2012
doi: 10.3389/fnagi.2012.00007

Route repetition and route retracing: effects of cognitive aging

Jan M. Wiener*, Hana Kmecova and Olivier de Condappa

Psychology Research Centre, Bournemouth University, Poole, UK

Edited by:
Thomas Wolbers, University of Edinburgh, UK

Reviewed by:
Denise Head, Washington University in St. Louis, USA
John Philbeck, The George Washington University, USA

****Correspondence:***
Jan M. Wiener, Psychology Research Centre, Bournemouth University, Poole House, Talbot Campus, Fern Barrow, Poole, Dorset BH12 5BB, UK.
e-mail: jwiener@bournemouth.ac.uk

Retracing a recently traveled route is a frequent navigation task when learning novel routes or exploring unfamiliar environments. In the present study we utilized virtual environments technology to investigate age-related differences in repeating and retracing a learned route. In the training phase of the experiment participants were guided along a route consisting of multiple intersections each featuring one unique landmark. In the subsequent test phase, they were guided along short sections of the route and asked to indicate overall travel direction (repetition or retracing), the direction required to continue along the route, and the next landmark they would encounter. Results demonstrate age-related deficits in all three tasks. More specifically, in contrast to younger participants, the older participants had greater problems during route retracing than during route repetition. While route repetition can be solved with egocentric response or route strategies, successfully retracing a route requires allocentric processing. The age-related deficits in route retracing are discussed in the context of impaired allocentric processing and shift from allocentric to egocentric navigation strategies as a consequence of age-related hippocampal degeneration.

Keywords: route retracing, route learning, cognitive aging, spatial memory, wayfinding

INTRODUCTION

Age-related differences in navigation abilities are well established both in animal and human literature (Rosenzweig and Barnes, 2003; Moffat, 2009). While age-related performance declines have been reported for different navigation tasks, they seem to be particularly pronounced in unfamiliar environments (Devlin, 2001). One navigation ability crucial for navigating unfamiliar environments is retracing—navigating a recently traveled route from the end to the start—as it enables a navigator to return to a known part of the environment (Lorenz, 1952; Miller and Eilam, 2011). Specific age-related deficits in route retracing would increase the risk of getting lost when navigating novel environments and could thus explain why older adults often report avoiding unfamiliar places and routes (Burns, 1999). While route retracing is a common navigation task, especially when exploring unfamiliar environments, it has received surprisingly little attention in the literature and it is unclear how it is accomplished. In the current study we present a novel experimental paradigm to investigate the cognitive processes and strategies involved in route learning and route retracing in more detail. Moreover, by comparing route retracing performance between a younger and older age group we investigate the effects of cognitive aging on route retracing.

Route knowledge is typically conceptualized as a series of stimulus-response associations (Trullier et al., 1997). A single stimulus-response association consists of recognizing the current place (e.g., by recognizing a landmark associated with that place) and selecting the direction in which to proceed along the route (Waller and Lippa, 2007). Learning a route with multiple decision points, therefore, requires knowledge of landmarks along the routes, associations of directional information with these landmarks, and knowledge about the order of landmarks.

Note that route knowledge that takes the form of stimulus-response pairs is inherently uni-directional, allowing a route to be repeated. The stimulus-response pairs are encoded in an egocentric reference frame during learning ("Turn left at X"). During route retracing, however, the decision points are approached from a viewpoint different to that experienced before. Accordingly, the egocentric stimulus-response pairs that were encoded during route learning do not support route retracing. Route retracing requires knowledge about the spatial relationship between the direction from which a decision point is approached and the direction in which the route proceeded. Such a representation is viewpoint independent—i.e., allocentric—and would support for route retracing.

Egocentric and allocentric navigation strategies are supported by different neuronal circuits: egocentric strategies involve the parietal cortex and the caudate nucleaus, while allocentric strategies are hippocampus dependent (McDonald and White, 1994; Wolbers et al., 2004; Burgess, 2008). While cognitive aging affects egocentric strategies (Barrash, 1994; Wilkniss et al., 1997; Moffat et al., 2001; Head and Isom, 2010), allocentric strategies seem to be more severely affected (Begega et al., 2001; Moffat and Resnick, 2002). As a result, a number of studies report shifts from allocentric to egocentric strategies with increasing age (Barnes et al., 1980; Nicolle et al., 2003; Rodgers et al., 2012; Wiener et al., under review). Age-related hippocampal degeneration offers an explanation for the impaired allocentric processing and according strategy shifts (Raz et al., 2010).

In the current study we used a novel experimental paradigm to investigate the cognitive processes and strategies involved in route retracing. Specifically, we tested the hypothesis that route retracing, in contrast to route repetition, relies on allocentric processing. In the experiment, participants were navigated along a complex route with multiple decision points each featuring a unique landmark. In the subsequent test phase they were guided along sections of the route either in the direction of original travel (route repetition) or in the opposite direction (route retracing). Their tasks were, first, to indicate travel direction (route repetition or route retracing), second to indicate the direction required to continue along the route to either reach the end or the start place (depending on travel direction), and third, to identify the next landmark encountered on route if the current travel direction was maintained. Comparisons of performance in these tasks between route repetition and route retracing trials allowed for first insights into the nature of route retracing. In order to test whether route retracing in fact involves allocentric processing, we compared performance between a younger and older participant group. In line with earlier research into the effects of cognitive aging on navigation abilities (Moffat et al., 2001; Head and Isom, 2010), we expected an overall effect of age on performance in all three tasks. If route retracing—as argued above—relied on allocentric processing, we expected additional age-related performance declines for route retracing trials as compared to route repetition trials reflecting the particularly adverse effects of cognitive aging on allocentric navigation strategies (Moffat and Resnick, 2002; Iaria et al., 2009).

MATERIALS AND METHODS

PARTICIPANTS

Forty participants [20 younger (eight females; mean age 20.53 ± 1.84 years, range 25–30); 20 older (11 females; mean age 69.45 ± 5.48 years, range 61–85)] took part in the experiment. The montreal cognitive assessment (MoCA; Nasreddine et al., 2005) was administered to all participants to screen for mild cognitive impairment (MCI). No participant had to be excluded based on the recently recommended MoCA cut-off score for the MCI of 23 (Luis et al., 2009). The average MoCA scores for the young and old age group were 27.56 (young) and 27.65 (old).

THE VIRTUAL ENVIRONMENT

Using Vizard 3.0 (WorldViz) we created a virtual route consisting of 11 four-way intersections (see **Figure 1**). Each intersection could be identified by a unique single landmark—an image of an object—that was mapped onto a cube suspended from the wall. During the experiment, participants were passively transported along the entire route in the training phase and along parts of the route in the test phase.

PROCEDURE

The experiment consisted of six experimental sessions. Each experimental session was composed of a training phase and a test phase. In the training phase, participants were transported along the entire route twice. Their task was to memorize the route. The test phase consisted of 18 trials, each of which was composed of three tasks:

- **Route Direction Task.** First, participants were transported along two intersections of the original route either in the same direction as during training (route repetition, nine trials) or in the opposite direction (route retracing, nine trials). For example, in a route repetition trial they would approach the intersection with the sofa, turn left and then approach the intersection with the football where movement stopped (see **Figure 1**). Participants were asked to indicate the direction of

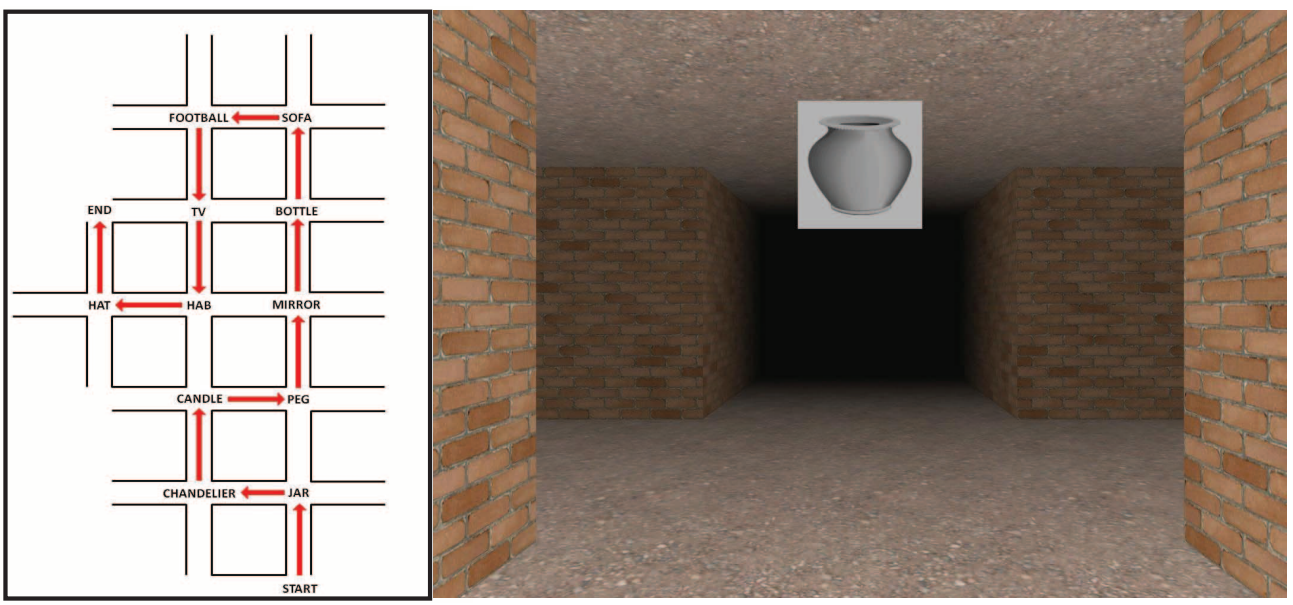

FIGURE 1 | Left: schematic drawing of the route consisting of 11 intersections; **right:** screen-shot of one of the intersections.

travel (repetition or retrace). Participants were instructed to respond as soon as they identified the travel direction, even if this occurred during the actual movement. Chance level for this task was 50%.

- **Intersection Direction Task.** Subsequent to the *Route Direction Task*, participants were asked to indicate the direction in which the route continued after movement stopped given the current travel direction. For route repetition trials, this involves indicating the direction required to follow the original route toward the end. In contrast, for route retracing trials this involves indicating the direction required to return to the start location while remaining on the route. With three possible movement directions and an equal amount of trials requiring a left, right, and straight responses, chance level for this task was 33.3%.
- **Landmark Sequence Task.** Finally, participants were presented with an image depicting three of the landmarks on the route. Their task was to indicate which of these landmarks would be encountered next, if the current travel direction was maintained. Chance level for this task was 33.3%.

Participants were instructed to respond as accurately and as quickly as possible by pressing the correspondingly labeled buttons on a response box (Cedrus RB-730).

The *Route Direction Task*, the *Intersection Direction Task*, and the *Landmark Sequence Task* were designed to test different aspects of route learning and route retracing. To solve the *Route Direction Task* participants needed to compare the sequence of landmarks and/or turns encountered during travel with their route memory. The *Intersection Direction Task* and the *Landmark Sequence Task* require participants to anticipate the upcoming movement direction or the next landmark, respectively. For repetition trials, these tasks are functionally equivalent to standard route learning tasks (Waller and Lippa, 2007; Head and Isom, 2010). Retracing trials, in contrast, require further processing: the *Landmark Sequence Task* requires manipulation of the temporal order of the landmarks; the *Intersection Direction Task* requires comprehending the spatial relationships between the direction from which an intersection is approached and the direction in which the route continues.

ANALYSIS

We first analyzed performance for the *Route Direction Task*. Only trials in which participants correctly identified travel direction were included in the analyses of the *Intersection Direction* and the *Landmark Sequence Task*. As a result of removing incorrect *Travel Direction Task* trials, fewer data points were available for the remaining analyses. In order to analyze effects of learning on these two tasks we, therefore, pooled data from sessions 1–3 and 4–6.

RESULTS

ROUTE DIRECTION TASK

In order to enter the final data-set, participants' performance in repetition trials on the *Route Direction Task* had to exceed chance level (50%). This criterion was set to ensure that participants had acquired sufficient route knowledge during the training phases to investigate the effects of cognitive aging on route repetition. Performance for two older participants did not reach chance level. These participants were excluded from the final data-set.

To examine the impact of travel direction (route repetition and route retracing) on performance in the Route Direction Tasks between age groups, a repeated-measures ANOVA was conducted with the between-subject factors of age group (young, older) and sex and two within-subject factors of experimental session (1–6) and travel direction (repetition, retrace). We observed main effects of age [$F_{(1,\ 34)} = 9.74$, $p < 0.01$, $\eta^2 = 0.22$], session [$F_{(3.2,\ 111.17)} = 42.20$, $p < 0.001$, $\eta^2 = 0.55$], direction [$F_{(1,\ 34)} = 26.36$, $p < 0.001$, $\eta^2 = 0.44$], but not of sex [$F_{(1,\ 34)} = 0.16$, $p = 0.69$, $\eta^2 = 0.01$]. Specifically, younger participants performed better than older participants (86.19% vs. 74.97%), performance on repetition trials was better than on retracing trials (88.08% vs. 73.07%), and performance improved over experimental sessions (session 1: 60.96%, session 6: 89.94%).

The main effect of direction was primarily driven by the impaired performance of older participants on retracing trials (see **Figure 2**). This is reflected in the significant interaction of direction *x* age group [$F_{(1,\ 34)} = 10.31$, $p < 0.01$, $\eta^2 = 0.23$] and by *post-hoc* tests demonstrating that younger and older participants performed comparatively during route repetition trials [*t*-test (89.31% vs. 87.25%): $t_{(35.75)} = 0.73$; $p = 0.47$], but performed differently during route retracing trials [*t*-test (84.27% vs. 63.32%): $t_{(23.50)} = 3.59$; $p < 0.01$]. Only one other interaction, direction *x* session [$F_{(2.9,\ 100.7)} = 3.55$, $p = 0.02$, $\eta^2 = 0.10$] was significant.

Note that participants who entered this analysis were selected on basis of their performance on repetition trials. However, despite good performance on repetition trials, older adults showed impaired performance on retracing trials compared to young adults. In other words, the subsample of older adults that had no problems identifying travel direction during route repetition, exhibited a specific age-related impairment when traveling in the opposite direction along the route.

How did participants solve the *Route Direction Task*? In principle there are two ways: first, participants can compare the order in which the landmarks are encountered during training and test phase; second, for those test trials that feature a turn at the first intersection encountered, participants can compare the turning direction at this intersection between training and test. The analysis of response times for test trial with a turn at the first intersection allows us to distinguish between these two alternatives: Turning onset was 4.7 s after the test trial started. After 7.4 s the landmark of the second intersection was in sight. Response time for the relevant test trials was 10.25 s for young adults, 12.08 s for older adults, 11.06 s for repetition trials, and 11.26 s for retracing trials. There was a main effects of age [$F_{(1,\ 36)} = 8.33$, $p < 0.01$, $\eta^2 = 0.19$] but no main effect of direction [$F_{(1,\ 36)} = 1.91$, $p = 0.18$, $\eta^2 = 0.05$] and no significant interaction [$F_{(1,\ 36)} = 1.52$, $p = 0.23$, $\eta^2 = 0.04$] (see **Figure 2** right). Participants made their decision 3 s (younger) to 5 s (older) after the second landmark was in sight. This strongly suggests that participants analyzed the order in which landmarks were encountered during travel to inform their decision, rather than the turning direction at the first intersection encountered.

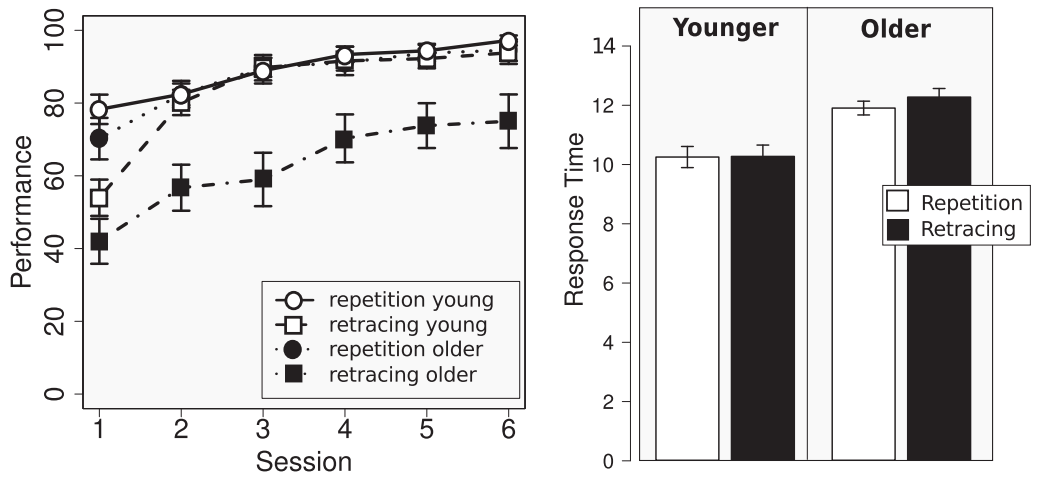

FIGURE 2 | Left: performance for the *Route Direction Task*; **right:** response time for test trials featuring a turn at the first intersection encountered.

INTERSECTION DIRECTION TASK

As a result of removing two older participants from the final dataset and of excluding data from incorrect *Route Direction Task* trials from the further analysis, fewer trials from older participants (1446) than from younger participants (1720) entered the analysis of the *Intersection Direction Task* and the *Landmark Sequence Task*.

In order to examine performance differences between age groups in the *Intersection Direction Task*, a repeated-measures ANOVA was conducted with the between-subject factor of age (younger, older) and two within-subject factors of experimental session (first and second half of the experiment) and movement direction (repetition, retrace). We observed main effects of session [$F_{(1,\ 36)} = 29.76$, $p < 0.001$, $\eta^2 = 0.45$], direction [$F_{(1,\ 36)} = 29.51$, $p < 0.001$, $\eta^2 = 0.45$], and age [$F_{(1,\ 36)} = 17.39$, $p < 0.001$, $\eta^2 = 0.33$]. The main effect of age was driven both by repetition trials (*post-hoc*: $p < 0.001$) and by retracing trials (*post-hoc*: $p < 0.01$).

Of the interactions only direction x session [$F_{(1,\ 36)} = 9.07$, $p < 0.01$, $\eta^2 = 0.20$] and direction x session $\times$ age group [$F_{(1,\ 36)} = 4.12$, $p = 0.05$, $\eta^2 = 0.10$] were significant. These interactions were primarily driven by impaired learning in the older adults in the retracing trials: while young participants' performance improved over the course of the experiment for both repetition and retracing trials, the older adults' performance improved only on repetition trials, but not on retracing trials (see **Figure 3**). This is corroborated by additional separate repeated-measures ANOVAs for the young and the old age group: while main effects of direction and session were observed for both age groups (all $p < 0.05$), the interaction between direction and session was significant only in the older age group ($p = 0.02$), but not in the young age group ($p = 0.12$).

Note that performance for retracing trials in the older age group remained close to chance level performance (33%) for the entire experiment (see **Figure 3**).

LANDMARK SEQUENCE TASK

In order to examine performance differences between age groups in the *Landmark Sequence Task*, a repeated-measures ANOVA was conducted with the between-subject factor of age (younger, older) and two within-subject factors of experimental session (first and second half of the experiment) and movement direction (repetition, retrace). We observed main effects of age [$F_{(1,\ 36)} = 11.54$, $p < 0.01$, $\eta^2 = 0.24$] and session [$F_{(1,\ 36)} = 95.07$, $p < 0.001$, $\eta^2 = 0.73$], but not of direction [$F_{(1,\ 36)} = 2.30$, $p = 0.14$, $\eta^2 = 0.04$]. Overall, performance was better for the young age group (young: 76.20%; old: 63.31%) and increased over the course of the experiment (first half: 62.22%; second half: 77.29%; see **Figure 3**). While none of the interactions was significant, the direction x age group interaction neared significance [$F_{(1,\ 36)} = 4.04$, $p = 0.052$, $\eta^2 = 0.10$].

DISCUSSION

In this study we used a novel experimental paradigm to investigate the effects of cognitive aging on the ability to retrace a route—i.e., to navigate from the end of a route back to the start location. In the experiment, participants first viewed a visual presentation of a route and were then presented with short segments of the route either in the direction experienced during training (route repetition trials) or in the opposite direction (route retracing trials). For each of these presentations, participants were given three tasks: in the *Route Direction Task* they had to indicate the overall travel direction; in the *Intersection Direction Task*, they had to indicate the direction of movement required to remain on the route given the current travel direction; in the *Landmark Sequence Task* they had to indicate which landmark they would encounter next when proceeding in the current travel direction.

Consistent with earlier findings (Barrash, 1994; Wilkniss et al., 1997; Moffat et al., 2001; Head and Isom, 2010), the older age

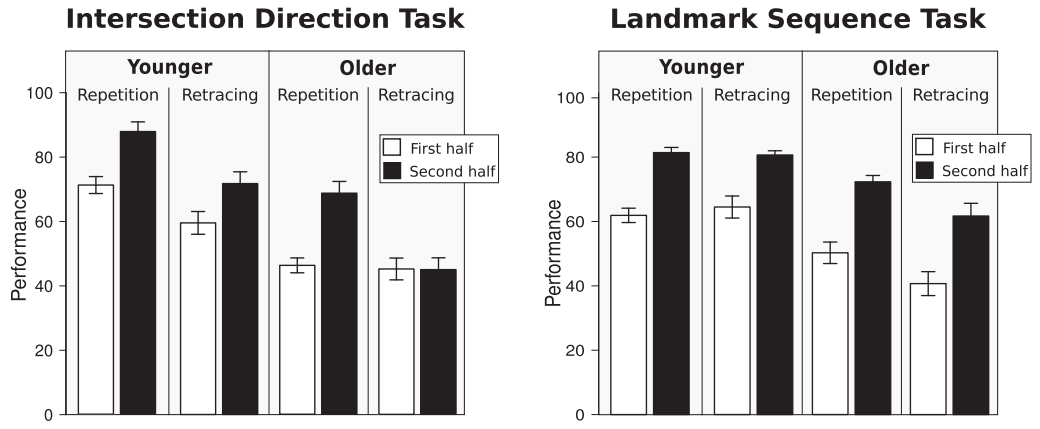

FIGURE 3 | Left: performance for the *Intersection Direction Task*; **right:** performancre in the *Landmark Sequence Task*.

group showed an overall performance deficit in route learning, even after removing two participants from the final data-set who did not reach chance level performance in route repetition trials in the *Route Direction Task*. In addition, older adults also showed specific deficits in retracing trials for both the *Route Direction Task* and the *Intersection Direction Task*. That is, older adults experienced difficulties when asked to identify the overall travel direction and to indicate the next movement direction when retracing the route, but not when repeating the route. Given the importance of successfully retracing a recently navigated route when exploring unfamiliar environments (Lorenz, 1952; Miller and Eilam, 2011), these effects offer an explanation for why age-related declines in navigation abilities are more striking in novel than in familiar environments (Devlin, 2001) and why older adults often report avoiding unfamiliar routes and places (Burns, 1999). In the following we consider results from the three tasks in the test phase in more detail.

ROUTE DIRECTION TASK

The *Route Direction Task* assessed participants' ability to identify the current travel direction (route repetition or route retrace) while being passively transported along a short segment of the route. While this task can, in principle, be solved by comparing the turning direction at a single intersection during test with that experienced during training, participants of both age groups only responded after they encountered a second landmark. This suggests that they used the temporal ordering of landmarks to solve the task. Both younger and older adults performed well on route repetition trials. In contrast, for route retracing trials we found performance decrements in the older age group. In other words, while the older adults that entered the final data-set were perfectly able to recognize travel direction when it was identical to that during training, they had problems doing so when travel direction was reversed. This may be explained by the involvement of different cognitive processes during route repetition and route retracing: in the *Route Direction Task* participants are asked to identify travel direction by matching the order of landmarks experienced during the test phase to that experienced during training. Research in the area of sequence processing suggests that in repetition trials this task recruits a supervisory process that involves monitoring and selectively activating relevant items while suppressing irrelevant ones (Oberauer et al., 2000). For retracing trials, however, the sequence is reversed thus additionally requiring the coordination of the relative positions between the items. The efficiency of this coordination process has been found to be affected by cognitive aging (Bopp and Verhaeghen, 2007) which could explain the specific impairment for retracing trials in the older age group.

LANDMARK SEQUENCE TASK

Older adults were also less accurate than young adults in the *Landmark Sequence Task* (see also Lipman and Caplan, 1992; Wilkniss et al., 1997; Head and Isom, 2010). However, the older adults reached performance levels clearly above chance level and performance increased over the course of the experiment. We did not observe a main effect of travel direction for the *Landmark Sequence Task*: both age groups performed at similar levels on repetition trials and on retrace trials. This seems surprising at first glance, but can be explained by (1) both the *Route Direction Task* and the *Landmark Sequence Task* requiring comparison between the temporal ordering of landmarks during the training phase with that experienced during the test phase; and (2) that only the data from correct *Route Direction Task* trials entered the *Landmark Sequence Task* analysis. In other words, as both tasks rely on similar processes and by pre-selecting trials on basis of performance in one task, potential effects of travel direction in the second task are reduced.

INTERSECTION DIRECTION TASK

In line with earlier research (e.g., Head and Isom, 2010), older adults were less accurate in the *Intersection Direction Task* than young adults. This effect was observed both for route repetition trials as well as for route retracing trials. In addition, we found a specific learning deficit in retracing trials for the older age

group: performance in retracing trials was close to chance level and, in contrast to repetition trials and the younger age group, did not improve over the course of the experiment. That is to say, not only did older adults perform weaker in indicating the correct direction when retracing a route, they were also unable learn the correct direction over the course of the experiment.

Egocentric route learning strategies (Trullier et al., 1997; Waller and Lippa, 2007) enable a navigator to solve the *Intersection Direction Task* in route repetition trials. Route retracing, in contrast, is not supported by egocentric strategies as intersections are approached from a different direction than during training. Route retracing, therefore, requires abstracting from the viewpoint-dependent memory encoded during the learning phase. This can be achieved by encoding the spatial relationship between the arm from which a particular intersection was approached and the arm in which the route proceeded. This form of representation is independent of the navigator's viewpoint and, therefore, allocentric. Recent research suggests that age-related deficits in allocentric processing (Moffat and Resnick, 2002; Moffat et al., 2007; Harris and Wolbers, in press) result from hippocampal degeneration during typical aging (Raz et al., 2010; Wiener et al., under review). This could also explain the age-related decline in performance on route retracing trials as these, in contrast to the route repetition trials, require allocentric processing.

In addition to the proposed deficits in allocentric processing resulting from age-related hippocampal degeneration, more general age-related declines in working memory and processing speed may contribute to the observed effects. The *Processing Speed Theory* states that declines in processing speed with increasing age can result in impairments in cognitive performance (Salthouse, 1996). This may be due to task-related time limitations or because results of earlier cognitive operations are no longer available when later operations are completed (simultaneity). While the current paradigm did not impose time limitations, allocentric processing is computationally more demanding than egocentric processes as it requires additional cognitive operations (Byrne et al., 2007). Any age-related processing speed effects are, therefore, more likely to affect retracing trials which rely on allocentric processing rather than repetition trials for which egocentric processes are sufficient.

We have argued that route retracing relies on allocentric processing. This is supported by a series of findings: route retracing provides a means to return to the start of a journey and has, therefore, been suggested to be crucial for exploring novel environments (Lorenz, 1952). Accordingly, in freely exploring rodents, route retracing is mainly observed during early stages of learning an environment (Miller and Eilam, 2011). Early stages of spatial learning primarily rely on allocentric place strategies, whereas egocentric response or route strategies only occur later (Tolman et al., 1946; Ritchie et al., 1950). Together with results from the current study this suggests that route retracing during the early stages of learning an environment relies on allocentric strategies.

Recent electrophysiological findings in rats suggest a neuronal mechanism that could support route retracing. Foster and Wilson (2006) recorded from hippocampal place cells and found that immediately after traversing a track, the hippocampal place cell activity observed during navigation was reactivated in reverse temporal order as if retracing the route. Importantly, these reverse replays were observed to a greater extent after navigating through a novel environment compared to a familiar environment, suggesting that such replays play an important role during spatial learning (see also Colgin and Moser, 2006).

To conclude, we have demonstrated age-related deficits in route retracing. Specifically, older participants showed impaired performance in both recognizing travel direction when navigating along the route in the reverse direction and in indicating the direction required to retrace the route. Given the importance of route retracing for learning novel environments these findings provide further insights into the effects of normal cognitive aging on wayfinding and orientation abilities.

ACKNOWLEDGMENTS

Many thanks to Gemma Hanson for her help in collecting data.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 March 2012; accepted: 06 May 2012; published online: 21 May 2012.

*Citation: Wiener JM, Kmecova H and de Condappa O (2012) Route repetition and route retracing: effects of cognitive aging. Front. Ag. Neurosci. **4**:7. doi: 10.3389/fnagi.2012.00007*