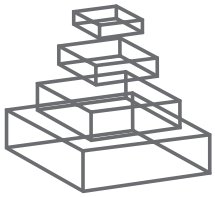
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RESEARCH TOPICS



LATERALIZATION AND COGNITIVE SYSTEMS

Topic Editors
Sebastian Ocklenburg, Christian Beste,
Onur Güntürkün and Marco Hirnstein

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LATERALIZATION AND COGNITIVE SYSTEMS

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Left-right asymmetries of structure and function are a common organization principle in the brains of humans and non-human vertebrates alike. While there are inherently asymmetric systems such as the human language system or the song system of songbirds, the impact of structural or functional asymmetries on perception, cognition and behavior is not necessarily limited to these systems. For example, performance in experimental paradigms that assess executive functions such as inhibition, planning or action monitoring is influenced by information processing in the bottom-up channel. Depending on the type of stimuli used, one hemisphere can be more efficient in processing than the other and these functional cerebral asymmetries have been shown to modulate the efficacy of executive functions via the bottom-up channel.

We only begin to understand the complex neuronal mechanisms underlying this interaction between hemispheric asymmetries and cognitive systems. Therefore, it is the aim of this Research Topics to further elucidate how structural or functional hemispheric asymmetries modulate perception, cognition and behavior in the broadest sense.

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Lateralization and cognitive systems

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Lateralization of brain and behavior in both humans and non-human animals is a topic that has fascinated neuroscientists since its initial discovery in the mid of the nineteenth century (Broca, 1861; Dax, 1865; Oppenheimer, 1977; Ströckens et al., 2013). Hemispheric asymmetries are abundant in the anatomy, neurochemistry and cytoarchitecture of the vertebrate brain and over the decades, a number of cognitive abilities have been shown to heavily rely on lateralized processing in the brain, the most widely investigated being language (Corballis, 2012; Ocklenburg et al., 2013b). Other cognitive domains that depend on lateralized processing include emotional processing (Önal-Hartmann et al., 2012), face and body perception (Thoma et al., 2014), spatial attention (Duecker et al., 2013), fine motor skills (Arning et al., 2013) and memory (Habib et al., 2003)—just to name a few. However, the impact of lateralization of brain function is not limited to these "classical" domains of lateralization research. The efficiency of higher cognitive processes in the vertebrate brain does not only depend on the involved cognitive systems themselves, but also on earlier information processing stages (Knudsen, 2007). Therefore, functional hemispheric asymmetries in stimulus processing can affect the efficiency of virtually any cognitive domain. This principle has recently been demonstrated for executive functions mediated by fronto-striatal networks, including working memory processes (Beste et al., 2010a,b, 2011, 2012). Ocklenburg et al. (2011, 2012) could show that the efficiency of executive functions like response inhibition or task switching is modulated when functional hemispheric asymmetries affect stimulus processing.

Based on these observations, the present Frontiers in Cognition Research Topic aimed to further investigate the relationship of lateralization and cognitive systems in the vertebrate brain. Overall, the Research Topic encompasses more than 30 novel publications, ranging from Original Research Articles to Reviews and Mini Reviews, Perspective Articles and Hypothesis and Theory Articles. From the beginning, the present Research Topic was conceptualized with a comparative multi-disciplinary inter-species approach in mind. This idea is reflected in the broad diversity of animal models included in the Research Topic, ranging from invertebrates (Frasnelli, 2013) to different species of birds (Manns and Ströckens, 2014; Rugani et al., 2014) and primates (Hopkins et al., 2014). In addition to animal research, several studies examined how lateralization impacts the functioning of different cognitive systems in the human brain. For example, it was investigated how handedness is related to other brain functions such as language lateralization (Carey and Johnstone, 2014), approach/avoidance motivation (Hardie and Wright, 2014), perceptual asymmetries (Marzoli et al., 2014), semantic priming (Fagard et al., 2014), response speed in the orthogonal Simon task (Iani et al., 2014) and cognitive performance in general (Prichard et al., 2013; Scharoun and Bryden, 2014). These studies are complemented by a review article investigating how twin studies could be useful in the quest to understand the complex interrelations of lateralization and cognitive systems (Ooki, 2014) as well as by a large-scale anatomical work investigating the effect of handedness on the structure of the cerebral cortex (Guadalupe et al., 2014). The relation of structural and functional asymmetries was also the topic of review article that investigated the cortical microstructural basis of lateralized cognition (Chance, 2014). Moreover, several authors investigated auditory lateralization (e.g., Specht et al., 2014). For example, Hirnstein et al. (2014a; Erratum in Hirnstein et al., 2014b) investigated how language lateralization measured with the Dichotic Listening Task relates to cognitive performance. The same task was used in a new smartphone version by Bless et al. (2013) who investigated the feasibility of conducting research on the interaction between lateralization and cognitive systems using a smartphone application. With more than 5500 article views and an AM score of more than 50 by the time this editorial was written, this article has gained more online attention than almost any other work published in Frontiers in Cognition. Other authors investigated visual lateralization (Asanowicz et al., 2013; Pellicano et al., 2013; Helon and Króliczak, 2014), asymmetries in emotional processing (Propper and Brunyé, 2013; Grimshaw and Carmel, 2014), behavioral lateralization (Morton, 2013; Corbetta et al., 2014), and asymmetries in face (Coronel and Federmeier, 2014) and body representation (Hach and Schütz-Bosbach, 2014), as well as in word generation (Meyer et al., 2014) and word recognition (Izura et al., 2014). Finally, some authors also investigated the impact of lateralized processing on executive functioning, the topic which had initially inspired this Research Topic (Marsh et al., 2013; Ocklenburg et al., 2013a; Kéïta et al., 2014; Stock and Beste, 2014).

Taken together, the wide variety of cognitive systems in different species covered in the present Research Topic highlights the enormous importance of understanding how and why the vertebrate brain is asymmetrically organized for almost any subfield within cognitive neuroscience. We hope that the excellent papers

assembled in the present Research Topic will help to stimulate more research aimed at understanding the complex mechanisms underlying the interaction between hemispheric asymmetries in stimulus perception and higher cognitive systems.

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Brain and behavioral lateralization in invertebrates

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Traditionally, only humans were thought to exhibit brain and behavioral asymmetries, but several studies have revealed that most vertebrates are also lateralized. Recently, evidence of left–right asymmetries in invertebrates has begun to emerge, suggesting that lateralization of the nervous system may be a feature of simpler brains as well as more complex ones. Here I present some examples in invertebrates of sensory and motor asymmetries, as well as asymmetries in the nervous system. I illustrate two cases where an asymmetric brain is crucial for the development of some cognitive abilities. The first case is the nematode *Caenorhabditis elegans*, which has asymmetric odor sensory neurons and taste perception neurons. In this worm left/right asymmetries are responsible for the sensing of a substantial number of salt ions, and lateralized responses to salt allow the worm to discriminate between distinct salt ions. The second case is the fruit fly *Drosophila melanogaster*, where the presence of asymmetry in a particular structure of the brain is important in the formation or retrieval of long-term memory. Moreover, I distinguish two distinct patterns of lateralization that occur in both vertebrates and invertebrates: individual-level and population-level lateralization. Theoretical models on the evolution of lateralization suggest that the alignment of lateralization at the population level may have evolved as an evolutionary stable strategy in which individually asymmetrical organisms must coordinate their behavior with that of other asymmetrical organisms. This implies that lateralization at the population-level is more likely to have evolved in social rather than in solitary species. I evaluate this new hypothesis with a specific focus on insects showing different level of sociality. In particular, I present a series of studies on antennal asymmetries in honeybees and other related species of bees, showing how insects may be extremely useful to test the evolutionary hypothesis.

Keywords: brain and behavioral lateralization, invertebrates, individual efficiency, directional asymmetry, evolutionary stable strategy, bee, sociality

INTRODUCTION

Until some decades ago, it was widely and incorrectly assumed that lateralization of structure and behavior was unique to the human brain, and having a lateralized brain was a mark of the cognitive superiority of humans. Now it is well known that most vertebrates have strong left–right asymmetries in their brain and in their behavior and lateralization is widespread in the vertebrate subphylum (for a review on handedness, see Ströckens et al., 2013; for a review on language lateralization, see Ocklenburg et al., 2013). Moreover, lateralization has a similar plan of organization in different species (for a review, see Rogers et al., 2013a). Recently, new evidence has shown the presence of lateralization in invertebrate species, suggesting that lateralization of the nervous system may be a feature of simpler brains as well as more complex ones (for a fully comprehensive review, see Frasnelli et al., 2012a). Some invertebrates show a lateralized behavior in motor control, other species exhibit asymmetries in several sensory modalities, such as in olfaction or vision, and in some cases behavioral lateralization seems to be correlated with a morphological one. In this section I present briefly some examples. In the second section I focus on two examples of brain asymmetries in invertebrates – fruit fly and nematode – that show how lateralization at the individual level is important to perform specific cognitive abilities. Then, in the third section, I explain that two patterns of lateralization exist, i.e., individual level and population level lateralization, I discuss how the latter may have evolved as an evolutionary stable strategy (ESS) and I focus on insects to provide evidence to test the ESS hypothesis. Finally, in the forth and last section, I conclude by comparing lateralization in invertebrates and vertebrates and discussing its possible evolutionary origins.

MOTOR ASYMMETRIES

Ants (*Formicidae*) and spiders (*Araneae*) were found to be lateralized (Heuts et al., 2003). A significant majority of spiders were observed to have mainly left leg lesions, and the process of catching them caused less severe leg lesions that were also significantly biased to the left. Similarly, Ades and Ramires (2002) showed that the spitting spider *Scytodes globula* (Arachnida, Araneae, Scytodidae) uses its left anterior legs considerably more frequently than the right anterior legs during prey handling. Twelve ant species of *Lasius niger* kept mainly to the right on their foraging "streets," whereas there was only one species that kept to the left (Heuts et al., 2003).

Behavior of the common American cockroach, *Periplaneta americana* (Linnaeus) has been investigated to determine whether lateralization is evident in a bias to turn left or right (Cooper et al., 2011). The cockroaches were allowed to run through a Y-tube and make a choice of which direction to take. Vanilla and ethanol were placed randomly at the ends of the Y-tube to entice the cockroaches to reach the end of the tubes. Thirty-eight adult cockroaches were tested for each of the following five conditions: both antennae intact, half of the left antenna cut, all of the left antenna cut, half of the right antenna cut, and all of the right antenna cut. Results showed that the odors of vanilla and ethanol play an insignificant role in the decision-making. Injury of one antenna affected the choice of direction, but not in a consistent way. While the majority of cockroaches with an amputated left antenna chose to go right, this did not happen when the entire right antenna was removed. In fact, similar injuries to either the right or the left antenna revealed an innate bias for turning right. Similar results were obtained when either antenna was cut in half. More evident was the skew towards the right path when both antennae were intact. The antennae of these gregarious insects are very long and, in addition to their role in detecting chemicals, they are very important as tactile organs (Okada and Toh, 2004). The study by Cooper et al. (2011) thus suggests that *Periplaneta americana* has a motor bias towards the right and not that this species is right-side dominant in its tactile and odor senses. Cockroaches turn right when there is no sensory input from the antennae, showing that they have a motor bias, and input from the antennae modifies this motor bias, often to reduce its strength.

Evidence of lateralized behavior has been found in the giant water bugs, *Belostoma flumineum Say* (Heteroptera: Belostomatidae; Kight et al., 2008). Giant water bugs are large aquatic insects, predators of other aquatic invertebrates, and small fishes. Bugs were trained to swim left or right in a T-maze and a significant preference to turn left, even when not reinforced, was observed, revealing a naïve bias in this species. To control for environmental cues that might bias the turning direction of water bugs in the maze, Kight et al. (2008) ran two separate experiments on independent groups of 20 water bugs. Both experiments were identical with the exception that, after the first group of 20 water bugs had been tested, the maze apparatus was rotated 180°, thereby reversing the polarity of all directional environmental cues such as lighting or electromagnetic fields. Again the same left turn tendency was observed. Hence, the explanation of the presence of this bias could be the existence of asymmetries in the nervous system or asymmetric exoskeletal morphology (i.e., leg length) that could cause biased swimming behavior.

PERCEPTUAL ASYMMETRIES

Fruit flies *Drosophila melanogaster* present a consistent asymmetry in the antenna-mediated flight control, in which the sensory signals coming from the left antenna contribute more to odor tracking than the sensory signals coming from the right antenna (Duistermars et al., 2009). The rapid odor lateralization in *Drosophila* is enabled by an asymmetric neurotransmitter release (Gaudry et al., 2013): each olfactory receptor neuron (ORN) spike releases ∼40% more neurotransmitter from the axon branch ipsilateral to the soma, as compared to the contralateral branch. This implies that, when an odor activates the antennae asymmetrically, ipsilateral central neurons begin to spike a few milliseconds before contralateral neurons, and ipsilateral central neurons also fire at a 30–50% higher rate. As a consequence, a walking fly can detect a 5% asymmetry in total ORN input to its left and right antennal lobes, and can turn toward the odor in less time than it requires the fly to complete a stride (Gaudry et al., 2013).

Red wood ants *Formica aquilonia* were found to use mainly their right antenna during "feeding" contacts where a "donor" ant exchanges food with a "receiver" ant through trophallaxis (Frasnelli et al., 2012b). Honeybees *Apis mellifera* seemed to use primarily their right eye for learning to associate a visual stimulus with a food reward (Letzkus et al., 2007).

Individual octopuses have significant eye preference for viewing a crab held outside the tank, but there is no population-level bias (Byrne et al., 2002, 2004).

An asymmetry in T-maze behavior has been reported in the cuttlefish *Sepia officinalis* trained to learn how to enter a dark, sandy compartment at the end of one arm of the maze (Alves et al., 2007). Eleven out of 15 cuttlefish displayed a pervasive side-turning preference. A further study by Alves et al. (2009) on a large sample ($N = 107$), confirmed the existence of a population-level bias. To find out whether or not visual perception plays a role in determining the direction of turning, cuttlefish were tested either inside the empty apparatus or with attractive visual stimuli (sand and shadow) on either sides of the T-maze. The authors (Alves et al., 2009) found that in both cases there was a preference to escape leftwards and they suggested that this left-turning bias results from an eye use preference. This visual lateralization observed in cuttlefish is task and age dependent (Jozet-Alves et al., 2012a). Cuttlefish were tested in a T-maze during postembryonic development (3, 7, 15, 30, and 45 days) in two different configurations of the apparatus, i.e., by providing or not shelters in the two choice arms of the maze to determine whether or not the direction of turning was stimulus dependent. Cuttlefish developed a left-turning bias from 3 to 45 days post-hatch (no bias at 3 or 7 days, bias at 15, 30, and 45 days) but only when shelters were provided in the apparatus (Jozet-Alves et al., 2012a). The left-turning bias is associated with a right visual hemi-field and thus a right eye preference. Cerebral correlates of this visual lateralization have been found by looking at anatomical (vertical lobe – VL, peduncle lobe – PL, inferior buccal and optical lobe – OL; Nixon and Young, 2003) and neurochemical (monoamines in OL) brain asymmetries and at their correlation with behavior (Jozet-Alves et al., 2012b) in cuttlefish at 3 and 30 days post-hatching. Brain and behavior asymmetries were present only at 30 days post hatching: a population level bias towards a larger PL and higher monoamine concentration (i.e., serotonin, dopamine, and noradrenaline) in the left OL was observed (Jozet-Alves et al., 2012b). Interestingly, there was a correlation with the behavioral results in the T-maze: the larger the right OL and the right part of the VL, the stronger the bias to turn leftwards. Jozet-Alves et al. (2012b) also observed one individual with the left OL larger and a bias to turn rightwards, which is evidence of a minority of cuttlefish lateralized in the opposite direction. Embryonic exposure to predator odor modulates visual

lateralization (Jozet-Alves and Hébert, 2013). A left-turning bias in T-maze for cuttlefish exposed to predator odor (sea-bass) prior to hatching was observed; whereas no bias for embryos exposed to non-predator odor (sea urchins) or for those incubated with no odor (blank tank) was found. Moreover, when tested with predator odor in the apparatus all cuttlefish display a left-turning preference, suggesting an ability to innately recognize predator odor (Jozet-Alves and Hébert, 2013).

In the deep-sea squid *Histioteuthis* the left eye and the left optic lobes are considerably larger than their equivalents on the right side (Wentworth and Muntz, 1989). The left eye appears to be used to look upwards into the better-lit upper waters, possibly to detect predators. The smaller right eye looks downwards, perhaps searching for bioluminescence, probably prey. Male squid *Sepioteuthis* can give courtship color displays to a female on one side, while giving a threat display to a male on the other side (Messenger, 2001). Asymmetrical color display is also a characteristic in cuttlefish (Brown et al., 2012). Male mourning cuttlefish (*Sepia plangon*) deceive rival males by displaying male courtship patterns to receptive females on one side of the body, and simultaneously displaying female patterns to a single rival male on the other (Brown et al., 2012). This evidence in cephalopods shows a capacity for considerable independence of motivational control on the two side of the central nervous system, a capacity that confers advantages on the individual.

FUNCTIONAL ASYMMETRIES

Limax slugs trained to avoid a particular food odor may hold the memory in either the right or the left procerebral division of the brain with the equal likelihood (Matsuo et al., 2010). However, when the right side is damaged by ablation, memory is fully affected, suggesting that learning and/or memory may be lateralized processes.

A behavioral asymmetry in mating behavior, due to an anatomical asymmetry dependent on a maternal effect gene, has been observed in the pond snail *Lymnaea stagnalis* (Asami et al., 2008; Davison et al., 2009). The pond snail *Lymnaea stagnalis* is a self-fertilizing hermaphrodite; in any single mating an individual takes the male role or the female role. Chirality in snails is determined by the single locus of the maternal effect (Boycott and Diver, 1923), i.e., the phenotype of an individual is dependent upon the genotype of their mother. Asami et al. (2008) used crossing experiments to demonstrate that the primary asymmetry of *L. stagnalis* is determined by the maternal genotype at a single nuclear locus where the dextral allele is dominant over the sinistral allele. Dextral is dominant in *Lymnaea* (by convention D = dextral allele; S = sinistral allele). The dextral and sinistral stocks are genetically DD or SS, respectively. On mating virgin sinistral and dextral types, offspring (F1 generation) that are genetically dextral (genotype = DS) but with a shell coil that is either sinistral (sinistral mother) or dextral (dextral mother) are produced (F1 generation). By allowing the sinistral F1 mother to self-fertilize, offspring that have a dextral coil, but are genetically DD, DS, or SS are produced (F2 generation). Dextral SS individuals were identified by virtue of their producing sinistral young. Davison et al. (2009) investigated the occurrence and the inheritance of a potential laterality trait in the pond snail and tried to understand whether laterality traits are associated with both body chirality and nervous system asymmetry. They found that all dextral "male" snails, both those paired with dextral and those paired with sinistral, circled in a counter-clockwise manner. Similarly, all the sinistral snails circled in a clockwise manner, regardless of whether they were paired with another dextral or a sinistral snail. The circling direction of the sinistral male was independent of the chirality of the female. It was instead entirely dependent on the maternal genotype, rather than the individual's own genotype.

Chirality in mating behavior is matched by an asymmetry in the brain. *L. stagnalis* has a ring of nine ganglia that form a central nervous system around the esophagus, with two more distant buccal ganglia on the buccal mass. In all dextral individuals, the right parietal ganglion is fused with the visceral ganglion and the left visceral ganglion is unpaired. By contrast, in all sinistral individuals the reverse is observed; the left parietal ganglion is formed by fusion with a visceral ganglion. The central nervous system in sinistral pond snails, therefore, has an asymmetry that is the reverse of that of dextral snails. As the coil of the shell is determined by the maternal chirality genotype and the asymmetry of the behavior is in accordance with this, it is likely that the same genetic locus, or a closely linked gene, determines the behavior. These findings suggest that the lateralized behavior of the snails is established early in development and is a direct consequence of the asymmetry of the body.

THE ADVANTAGES OF HAVING AN ASYMMETRICAL BRAIN

Irrespectively of the kind of asymmetry, having an asymmetrical nervous system seems to give the individual some advantages. Lateralized animals have been shown to outperform non-lateralized in many circumstances (McGrew and Marchant, 1999; Güntürkün et al., 2000; Rogers et al., 2004), suggesting that lateralization contributes significantly to biological fitness. A lateralized brain may confer several advantages: sparing neural tissue by avoiding duplication of functions in the two hemispheres (Levy, 1977); processing information in parallel (Rogers, 2002; Rogers et al., 2004); and preventing the simultaneous initiation of incompatible responses by allowing one hemisphere to have control over actions (especially in animals with laterally placed sensory organs, Andrew, 1991; Vallortigara, 2000). Moreover, Rogers (2000) suggested that enhanced cognitive ability is one of the potential benefits of cerebral lateralization because animals with strongly lateralized brains may have the ability to act directly on many sources of information at the same time. Lateralized individuals are better able to distinguish food grains from pebbles compared with non-lateralized individuals (Güntürkün et al., 2000), and this disparity is enhanced in the presence of predators (Rogers et al., 2004). Similarly, chimpanzees that fish for termites using one hand are more efficient than ambidextrous individuals (McGrew and Marchant, 1999). Recently, the influence of lateralization on problem solving by Australian parrots (eight species) has been examined (Magat and Brown, 2009). In both a pebble-seed discrimination test and in a string-pull problem, strongly lateralized individuals (those showing significant foot and eye biases) outperformed less strongly lateralized individuals, suggesting that cerebral lateralization conveys a significant foraging advantage and supporting the enhanced cognitive function hypothesis.

Interestingly, not only in vertebrates but also in invertebrates an asymmetric brain is crucial for the development of some cognitive abilities. Two examples of invertebrate species where brain asymmetry at the individual level can confer advantages to the individual and, moreover, is necessary for the animal to have some cognitive abilities, are provided by the fruit fly *D. melanogaster* and the nematode *Caenorhabditis elegans*.

THE FRUIT FLY *DROSOPHILA MELANOGASTER*

In the fruit fly, a structure located near the fan-shaped body connects the right and the left hemispheres (Heisenberg, 1994). This structure is an asymmetrical round body (called AB) with a diameter of about 10 μm and is not characteristic of all flies, since some flies have symmetry in this region. In a sample of 2,550 wild-type flies, 92.4% of individuals were found to have the AB in the right side of the brain (Pascual et al., 2004). Wild-type flies presenting symmetric structures were trained to associate an odor with an electric shock: a single training cycle was used for short-term memory testing and five individual training sessions (15-min rest intervals) for long-term memory testing. Pascual et al. (2004) observed no evidence of 4-day long-term memory in wild-type flies with a symmetrical structure, although their short-term memory was intact. On the contrary, flies with the asymmetrical structure formed long-term memory. Thus, brain asymmetry is not necessary for the *Drosophila* to establish short-term memory but it is important in the formation or retrieval of long-term memory.

THE NEMATODE *CAENORHABDITIS ELEGANS*

The second example concerns one of the smallest existing nervous systems, namely the nematode *C. elegans*. With its 302 neurons, the nematode offers a unique opportunity to address the manner in which symmetrical neuronal assemblies deviate to create functional lateralization. Hobert et al. (2002) have provided a detailed cellular and molecular description of left-right (L-R) asymmetry in the nervous system of *C. elegans*. In this species, 2/3 of the neurons (198 out of a total of 302) are present as bilaterally symmetrical pairs. Particularly intriguing components of L-R asymmetry in the *C. elegans* nervous systems are neuron pairs (or neuroblasts) that are bilaterally symmetrical in terms of their post-morphogenetic position, morphology and lineage, but at some point during embryogenesis, after bilaterality has been established, undergo L-R-specific sub-differentiation programs. This is the case of the Amphid Single-ciliated Endings, ASEL (left)/ASER (right) neurons that are the main taste receptors of *C. elegans*. ASEL and ASER are bilaterally symmetrical with regard to cell position, axon morphology, outgrowth and placement, dendritic morphology, and qualitative aspects of synaptic connectivity patterns. However, three putative sensory receptors of the guanylyl cyclase class, gcy-5, gcy-6, and gcy-7, are expressed asymmetrically in ASEL (gcy-6, gcy-7) and ASER (gcy-5), two to left and one to the right (Yu et al., 1997). This asymmetry of gene expression correlates with a significant functional asymmetry of the two neurons: laser-ablation studies revealed that each of the individual neurons is responsible for sensing a distinct class of water-soluble chemicals (Pierce-Shimomura et al., 2001). Ortiz et al. (2009) investigated the extent of functional lateralization of the ASE neurons and genes responsible for the left/right asymmetric activity of ASEL and ASER. They showed that a substantial number of salt ions are sensed in a left/right asymmetric manner and that lateralized responses to salt allow the worm to discriminate between distinct salt ions.

LATERALIZATION AT THE INDIVIDUAL AND AT THE POPULATION-LEVEL

In the two examples above lateralization at the individual level is fundamental for the individual to be able to perform some specific cognitive abilities, such as long-term memory formation in the fruit fly or discrimination of salt-ions in the nematode. However, it is worth emphasizing that behavioral (and brain) left-right asymmetries usually occur not only in single individuals but also in the same direction in most individuals. In this case, where most individuals show a similar direction of bias the group or population is biased, and so we speak of population-level lateralization. Individual brain efficiency does not require a definite proportion of left- and right-lateralized individuals. Thus, the arguments about the fact that brain lateralization increases individual efficiency do not explain population-level lateralization. Moreover, lateralization at the population level can also present ecological disadvantages, because it makes individual behavior more predictable to other organisms, such as predators. Theoretical models on the evolution of lateralization (Ghirlanda and Vallortigara, 2004; Vallortigara, 2006; Ghirlanda et al., 2009) suggest that the alignment of lateralization at the population level may have evolved as an ESS in which individually asymmetrical organisms must coordinate their behavior with that of other asymmetrical organisms (Vallortigara and Rogers, 2005). The hypothesis of the ESS of lateralization makes the quite straightforward prediction that initially "social" organisms would have started to be lateralized at the population-level, whereas "solitary" organisms retained lateralization at the individual level only.

INSECTS TO TEST THE EVOLUTIONARY STABLE STRATEGY THEORY

Invertebrates and in particular insects have been excellent models to test the hypothesis predicted by the theoretical models on the evolution of lateralization that directional (population-level) asymmetry should be found only in cooperative, social species (Anfora et al., 2010). In fact, insects are among the certain current-living species in which the distinction between solitary and gregarious behavior can be defined quite sharply with respect to at least some aspects of behavior and in which it is likely that no major changes in sociality have occurred in evolutionary terms. Thus, the comparison of lateralization in social and non-social insects may provide a powerful test for the theory (Ghirlanda and Vallortigara, 2004; Vallortigara and Rogers, 2005). In particular, among Hymenoptera closely related species have evolved either sophisticated eusociality or maintained solitary behavior.

THE HONEYBEE *APIS MELLIFERA*

Letzkus et al. (2006) first showed that honeybees *Apis mellifera* (Fam. Apidae, Tribe Apini – **Figure 1**) display laterality in learning to associate an odor with a sugar reward. The researchers used the proboscis extension reflex (PER) paradigm

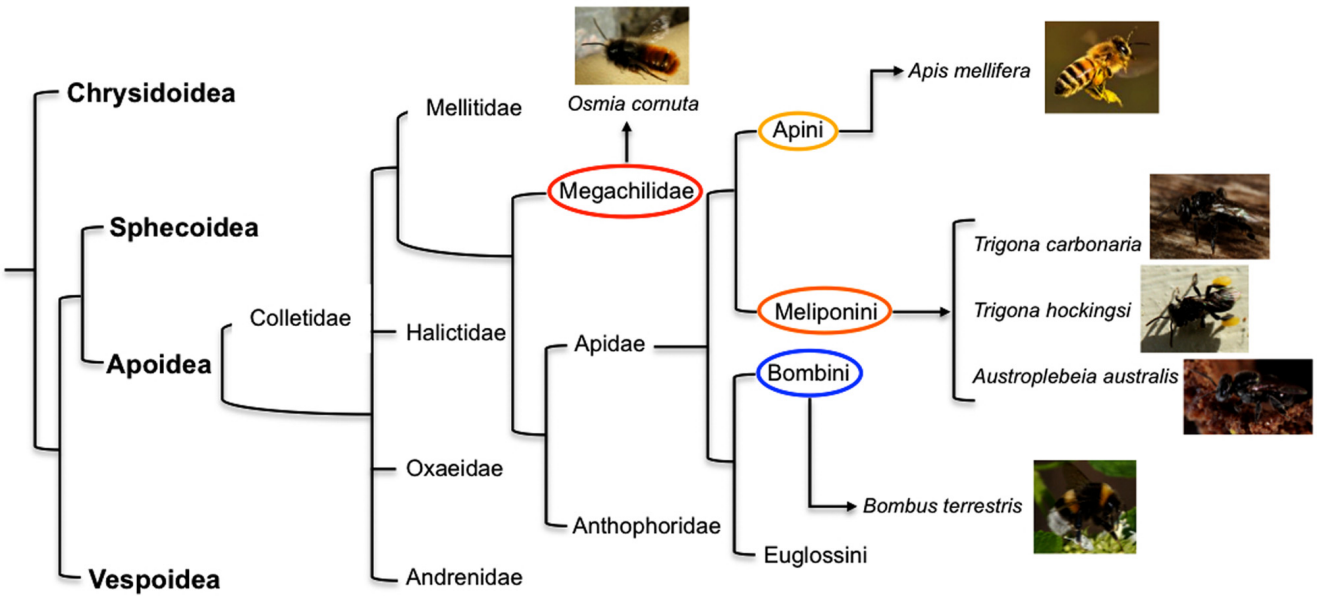


FIGURE 1 | A "family tree" for the Aculeata (hymenoptera with stings) showing the most likely relationship between super families (in Bold) and, for the super family Apoidea, the deduced lines of descent of some of the more common families of bees and tribes within the family Apidae (Michener, 1974). Highlighted are the tribes to which the species investigated for behavioral and brain asymmetries described in the current paper belong: in red the family Megachilidae (mason bee *Osmia cornuta*), in yellow Apini (honeybee *Apis mellifera*), in orange Meliponini (stingless bees *Trigona carbonaria*, *Trigona hockingsi*, *Austroplebeia australis*), and in blue Bombini (bumble bee *Bombus terrestris*).

(Bitterman et al., 1983), in which bees are conditioned to extend their proboscis when they perceive a particular odor that has been associated with a food reward. They tested three groups of bees: the bees in one group had their left antenna covered with a silicone compound, which prevents detection of odor, those in the second group had their right antenna covered, and those in the third group constituted a control in which both antennae were uncovered. Bees with the right antenna covered learned less well than the bees with their left antenna covered and bees with both antenna uncovered. Frasnelli et al. (2010b) duplicated the behavioral results of Letzkus et al. (2006) using forager Italian honeybees (*Apis mellifera ligustica* Spin.) and checked for morphological differences in the number of sensilla between the right and the left antenna. Results showed that putative olfactory sensilla (*placodea, trichodea, basiconica*) were significantly more abundant on the right antenna surface than on the left antenna surface (mean difference of 3%), whereas sensilla not involved in olfaction (*campaniformia, coeloconica, chaetica*) were more abundant on the left than on the right antenna surface (mean difference of 7%). However, it seems unlikely that this can account for the functional asymmetry.

Rogers and Vallortigara (2008) investigated whether lateralization could be found in recall of olfactory memory at various times after the bees had been trained using the PER paradigm. At 1–2 h after training, using both antennae, recall of short-term memory was possible only when the bee used its right antenna but at 23–24 h after training the long-term memory could be recalled only when the left antenna was in use. Hence, retrieval of olfactory learning is a time-dependent process, involving lateralized circuits. Moreover, Rogers and Vallortigara (2008) also checked whether the laterality was manifested as side biases to odors presented to the left or right side of the bee without coating of the antennae. Bees were trained with both antennae in use and the recall was tested 1, 3, 6, or 23 h after using lateral presentation of the stimuli instead of coating the antennae. At 1 h after training, the correct responses were higher when the odors were presented on the right side than on the left side. At 3 h after training, no significant left-right difference was observed. At both 6 and 23 h after training the correct responses were higher when the odors were presented on the left side than on the right side.

Frasnelli et al. (2010a) tested lateralized recall of olfactory memory in honeybees at 1 or 6 h after training using different odors, including a familiar appetitive odor (rose) as a negative stimulus and a naturally aversive odor (isoamyl acetate, IAA – alarm pheromone) as a positive stimulus. The results confirmed the finding by Rogers and Vallortigara (2008). Moreover, it was found that the dynamic of memory traces has marked consequences when odors are already known to the bees (either for a biological reason or as a result of previous experience) and are thus already present in the long-term memory store. As a result, response competition arising from multiple memory traces can be observed, with bees showing unexpected lack of specificity in their longer-term olfactory memories.

A strong odor dependence of the lateralization of short-term memory recall of odors has been reported in honeybees (Rigosi et al., 2011). After training with 1-octanol and 2-octanone, bees

showed no differences in the recall test regardless of whether they had use of only their right antenna, only their left antenna or both antennae. In contrast, bees trained with (−)-linalool showed a significant effect of the antenna in use: bees trained (and tested) with their right antenna in use performed significantly better than individuals with only their left antenna in use, whereas they performed the same as bees with both antennae in use (Rigosi et al., 2011). The odor (−)-linalool is one of the most common derivates of floral scents playing a crucial role as cue for pollinators (Knudsen et al., 1993). The odors 1-octanol and 2-octanone are unspecific and ubiquitous volatiles released from the green organs of the plants and thus of minor importance in pollinator plant interaction. Honeybees are able to learn complex odor mixtures by using a subset of key odors, such as (−)-linalool (Reinhardt et al., 2010) and, after conditioning bees to a mixture of odors (−)-linalool elicits higher levels of responding than do other components of the mixture presented singly (Laloi et al., 2000). Since bees are selective in their responses to odors, the strikingly different biological relevance of the odor compounds used by Rigosi et al. (2011) might be a reason for the observed difference in lateralization.

The asymmetry observed in the retrieval of olfactory learning in honeybee is much more complex than a difference in learning ability of the right and left antennae and the difference in number of olfactory sensilla is unlikely to explain entirely the behavioral laterality. Up to now, however, search for anatomical correlates of the asymmetry in higher centers of the bee brain has not revealed clear anatomical asymmetries (Haase et al., 2011a,b; Rigosi et al., 2011).

Sociality and lateralization in Apoidea

It is important to underline that the studies mentioned above conducted on eusocial honeybees found an olfactory asymmetry in learning and recall of memory that manifests itself as population-level bias (i.e., the same pattern of lateralization was found in most individuals). Anfora et al. (2010) compared the behavior and electrophysiological lateralization of olfactory responses in two species of the superfamily Apoidea, the social honeybee, *Apis mellifera* L. (Fam. Apidae), and the solitary mason bee, *Osmia cornuta* (Latreille; Fam. Megachilidae – **Figure 1**). Unlike honeybees, mason bees are solitary: every female is fertile and makes its own separate nest, they don't produce honey or wax and there are no workers (Nepi et al., 2005). Lateralization in mason and honeybees was tested using the PER paradigm. Bees were trained to associate an odor with a sugar reward and the recall of olfactory memory was tested at 1 h after training. The recall was better in honeybees when they used their right antenna than when they used their left antenna, confirming previous results obtained in the same species (Letzkus et al., 2006; Rogers and Vallortigara, 2008). Hence, honeybees show population-level lateralization. No such asymmetry was observed in mason bees. Consistent with this species difference, electroantennographic responses to a floral volatile compound and to an alarm pheromone were higher in the right that in the left antenna in honeybees but not in mason bees. Although the mason bees showed no population-level lateralization, they did show individual-level lateralization in that individual mason bees exhibited significant stronger responses either with the right or the left antenna, without any alignment of lateralization in the majority of the individuals. These data fit nicely with the hypothesis predicted by the theoretical models on the evolution of lateralization that links directional asymmetry with social behavior.

Olfactory asymmetries have been investigated also in bumblebees *Bombus terrestris* (Fam. Apidae, Tribe Bombini – **Figure 1**), an annual social species of bees. Anfora et al. (2011) ran a series of experiments similar to those conducted on mason and honeybees (Anfora et al., 2010). Bumblebees were trained to associate an odor with a reward using the PER paradigm and recall of memory was tested 1 h after. As for honeybees (Letzkus et al., 2006; Rogers and Vallortigara, 2008; Anfora et al., 2010; Frasnelli et al., 2010b), the bumblebees with the left antenna coated performed as well as those with both antennae in use, whereas bumblebees with the right antenna coated performed significantly less well. In contrast to honeybees, no significant differences were observed in electroantennographic responses between the left and right antennae of bumblebees when stimulated by two different compounds (an alarm pheromone and a floral scent). Interestingly, however, one class of bumblebee olfactory sensilla, *trichodea type A*, was shown to be more abundant on the surface of the right antenna than on the left one, and a slight tendency towards asymmetry was shown for a second class, i.e., *sensilla coeloconica*. Since electroantennographic responses represent the sum of responses of all ORNs housed in the sensilla of a single antenna (Schneider and Kaissling, 1957), the fact that morphological asymmetries were apparent only in a limited class of receptors may explain why, dissimilar to honeybees, no overall asymmetry was observed in EAG responses in bumblebees.

Kells and Goulson (2001) reported that bumblebees *Bombus* spp. show preferred directions of circling as they visit florets arranged in circles around a vertical inflorescence. In three (*Bombus lapidarius, Bombus lucorum*, and *Bombus pascuorum*) out of four species examined the majority of bumble bees circled in the same direction. Interestingly, the researchers did not observe any lateralization in *B. terrestris*. Since two species circled anticlockwise and one clockwise, it is unlikely that the asymmetry is a function of the structure of the florets.

Bumblebees observe and copy the behavior of others with regard to floral choices (Kawaguchi et al., 2007) and, moreover, they can learn to make nectar-robbing holes in flowers as a result of encountering them (Leadbeater and Chittka, 2008). Recently, Goulson et al. (2013) investigated handedness in nectar-robbing bumblebees (*Bombus wurflenii* and *Bombus lucorum*) feeding on *Rhinanthus minor*, a flower that can be robbed from either the right-hand side or the left-hand side and they looked at a possible effect of social learning on handedness. Numerous patches of *R. minor* spread across an alpine landscape were studied and each patch was found to be robbed on either the right or the left. The intensity of side bias increased through the season and was strongest in the most heavily robbed patches. Bees within patches seemed to learn robbing strategies (including handedness) from one another, either by direct observation or from experience with the location of holes, leading to rapid frequency-dependent selection for a common strategy, i.e., adopting the same handedness within particular flower patches.

Frasnelli et al. (2011) studied primitive social bees, stingless bees (Fam. Apidae, Tribe Meliponini – **Figure 1**) to shed light on the possible evolutionary origins of the left-right antennal asymmetry. Three species of Australian native, stingless bees (*Trigona carbonaria*, *Trigona hockingsi,* and *Austroplebeia australis*) were trained to discriminate two odors, lemon(+)/vanilla(−), using the PER paradigm. Recall of the olfactory memory at 1 h after training was better when the odor was presented to the right than to the left side of the bees. In contrast, recall at 5 h after training was better when the odor was presented to the left than to the right side of the bees. Hence, stingless bees (Meliponini) have the same laterality as honeybees (Apini), which may suggest that olfactory lateralization is likely to evolved prior to the evolutionary divergence of these species. The distributional pattern and fossil records are indicative of greater antiquity for the Meliponini compared to Apidi, Bombini, and Euglossini, and suggestive of an independent origin or an early divergence from a proto-other Apidae branch (Camargo and Pedro, 1992). However, the phylogenetic relationships among the four tribes of bees (i.e., corbiculate Apidae: Euglossini, Bombini, Meliponini, and Apini) are controversial and the single origin of eusociality is questionable. It has been suggested that eusociality evolved once in the common ancestor of the corbiculate Apidae, advanced eusociality evolved independently in the honeybee and in stingless bees, and that eusociality was lost in the orchid bees (Cardinal and Danforth, 2011). Considering this, it can be argued that the similarity found between honeybees and the three species of Australian stingless bees in population-level lateralization in recall of olfactory memory is linked with the social feature shared by the two tribes and may have evolved independently in the trajectory that led to honeybees and trajectory that led to stingless bees.

One can argue that the behavioral traits, such as olfactory learning and electroantennographic responsivity, investigated in the studies reported above (Rogers and Vallortigara, 2008; Anfora et al., 2010, 2011) are not obviously social in nature. However, it is not possible to exclude that the original drive for antennal asymmetries could be related to social interaction during for example trophallaxis, as observed in ants (Frasnelli et al., 2012b). Moreover, it is conceivable that some forms of asymmetries that are unlikely to have been directly selected as ESSs in social contexts could have evolved as population-level biases as by-product of other biases that in fact evolved as ESSs. It is likely that when an individual-level asymmetry is stabilized as a directional (population-level) asymmetry, other asymmetries that in principle would not require any alignment at the population level because they are irrelevant to any social interaction would organize themselves as directional as well simply because a directional organization in the two sides of the brain already exists.

Very recently Rogers et al. (2013b) investigated whether the rich social life of honeybees may be associated with directional biases in antennal use. Different social behavior (latency to contact, numbers of PER, number of C-responses, number of mandibulations) were analyzed in pairs of bees coming from either the same colony or from different colonies and having only their right antennae (left antennae removed) or only their left antenna (right antennae removed) or both antennae intact. The authors found a directional bias in the use of antennae for three measures of social interaction, latency, PER and C-responses. Dyads of bees tested using only their right antennae contacted after shorter latency and were significantly more likely to interact positively (proboscis extension) than were dyads of bees using only their left antennae. The latter were more likely to interact negatively (C-responses) even though they were from the same hive. In dyads from different hives C-responses were higher in dyads of bees using only their right antennae than in dyads of bees using only their left antennae. The right antenna seems, therefore, not only specialized for learning about new odors associated with food sources but also in exchange of odoriferous information between same-colony worker bees and in control of aggressive responses between different-colony worker bees. Use of the right antenna was also shown to motivate bees to approach and contact each other. In fact, although use of the left antenna did not cause bees to completely avoid each other, social behavior performed by the bees with only their left antennae intact was not context-appropriate, possibly due to an inability to distinguish between hive mates and bees from another hive. Hence, the right antenna seems to control social behavior appropriate to context, suggesting that lateral biases in behavior are associated with requirements of social life.

LATERALIZATION IN VERTEBRATES AND INVERTEBRATES: COMMON ANCESTOR OR CONVERGENT EVOLUTION?

All the evidence about differences in the specializations of the left and right sides of the nervous system and behavior in invertebrates suggests that invertebrates share the attribute of lateralization with many vertebrates. This strengthens the conclusion that lateralization provides substantial advantages, since it has persisted, or evolved many times, in such diverse groups of animals. Asymmetries in invertebrates and vertebrates sometimes also show similarities in their appearance. One example is the processes of memory formation in parallel on the right and left sides of the brain and the interaction between the right and left memory traces during memory formation. In fruitflies, the transition from short- to long-term records of conditioning depends on an asymmetric body normally only present on the right side of the brain. When there is also a counterpart on the left, only short-term memory is formed (see The Fruit Fly *Drosophila melanogaster*). In honeybees, recall of short-term memory is possible through the right side, whereas recall of long-term memory is possible through the left side (see The Honeybee *Apis mellifera*). A shift of recall access from one to the other side of the brain has been observed previously in birds (Cipolla-Neto et al., 1982; Clayton, 1993; Andrew, 1999). This suggests that lateralized events in memory formation may be similar in arthropods and vertebrates and that the shifts from recently acquired information held independently by the right and the left sides to more integrated and complete long-term records should constitute a considerable advantage. Thus, because of this advantage mechanisms controlling such shifts have evolved (probably independently) in both arthropods and vertebrates.

The difficult and complex issue is whether homologous genes in invertebrates and vertebrates determined lateralization or whether there has been analogous evolution of lateralized function in the

two taxa. It is probable that the common ancestor of metazoan animals specified the right-left axis (Vandenberg and Levin, 2009). Since it is also true of single-cell organisms such as ciliates, the same basic genetic mechanisms of specification of the left-right axis were probably present in the common ancestor of multicellular animals. The most striking evidence that the left-right axis may have been specified very early in metazoan evolution is the involvement of orthologs, i.e., homologous gene sequences in different species, of the Nodal family in the evolution of body plans and left-right specification in vertebrates (Boorman and Shimeld, 2002) and in Bilateria (Grande and Patel, 2009). The signaling molecule Nodal, a member of the transforming growth factor-β superfamily, is involved in the molecular pathway that leads to left-right asymmetry in vertebrates (Boorman and Shimeld, 2002) and in other deuterostomes, but no nodal ortholog had been reported previously in the two main clades of Bilateria: Ecdysozoa (including flies and nematodes) and Lophotrochozoa (including snails and annelids). Grande and Patel (2009) reported the first evidence for the presence of a nodal ortholog in a non-deuterostome group, indicating that the involvement of the Nodal pathway in left-right asymmetries might have been an ancestral feature of the Bilateria. Furthermore, this study suggests that nodal was present in the common ancestor of bilaterians and it too may have been expressed asymmetrically.

The recent comparison between the cellular and molecular mechanisms leading to neuronal asymmetries in the nematode *C. elegans* and in the zebrafish *Danio rerio* (Taylor et al., 2010) may also be helpful in the difficult and complex issue of the evolution of asymmetries in vertebrate and invertebrates. The specification of the left and right Amphid Wing "C" (AWC) neurons of the nematode olfactory system and the asymmetry in the fish epithalamus has been analyzed. It has been shown that both species use iterative cell–cell communication, i.e., reciprocal interactions between neural cells rather than a simple linear pathway, to establish left-right neuronal identity, and this reinforces the left-right asymmetry but with different outcomes and molecular details in each species. The functional differences in morphologically identical neurons in the olfactory system of *C. elegans* are the result of gap-junctional communication and calcium influxes, whereas the neuroanatomical left-right differences in the epithalamus of *D. rerio* are the result of morphogenic changes regulated by secreted signaling molecules. Thus, the invertebrate and vertebrate species considered share some commonalities in the mechanisms involved in asymmetrical neural development, i.e., the interaction of neurons across the midline during formation of the asymmetrical nervous system, and the inherently stochastic nature of some developmental pathways. However, results need to be interpreted with caution since the evolutionary gap between the 302 neurons of the worm and the estimated 78,000 neurons of the larval fish (Hill et al., 2003) is considerable. The striking differences in the genetic and cellular pathways underline the improbability that nematode and zebrafish lateralization arose from the same ancestral event. It is instead more reasonable to hypothesize that the left-right differences in the two species have evolved by convergence.

The ESS theory predicts that lateralization at the population-level is more likely to have evolved in "social" rather than in "solitary" species. Studies conducted in different species of insects seem to be in alignment with this prediction. Shoaling and not-shoaling fishes have also provided evidence in support of this hypothesis. In 20 species of teleost fishes, Bisazza et al. (2000) found that the shoaling ones ("social") were lateralized for turning bias at the population-level; whereas the not shoaling ones were lateralized at the individual level but non at the population level (Bisazza et al., 2000; Vallortigara and Bisazza, 2002). Although lateralization in invertebrates may not be related to lateralization in vertebrates in an evolutionary sense, the social pressures associated with the need to coordinate asymmetric behaviors would hold irrespective of whether lateralization in vertebrates and invertebrates represent homology (common ancestor) or homoplasy (convergent evolution).

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Functional and structural comparison of visual lateralization in birds – similar but still different

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Vertebrate brains display physiological and anatomical left-right differences, which are related to hemispheric dominances for specific functions. Functional lateralizations likely rely on structural left-right differences in intra- and interhemispheric connectivity patterns that develop in tight gene-environment interactions. The visual systems of chickens and pigeons show that asymmetrical light stimulation during ontogeny induces a dominance of the left hemisphere for visuomotor control that is paralleled by projection asymmetries within the ascending visual pathways. But structural asymmetries vary essentially between both species concerning the affected pathway (thalamo- vs. tectofugal system), constancy of effects (transient vs. permanent), and the hemisphere receiving stronger bilateral input (right vs. left). These discrepancies suggest that at least two aspects of visual processes are influenced by asymmetric light stimulation: (1) visuomotor dominance develops within the ontogenetically stronger stimulated hemisphere but not necessarily in the one receiving stronger bottom-up input. As a secondary consequence of asymmetrical light experience, lateralized top-down mechanisms play a critical role in the emergence of hemispheric dominance. (2) Ontogenetic light experiences may affect the dominant use of left- and right-hemispheric strategies. Evidences from social and spatial cognition tasks indicate that chickens rely more on a right-hemispheric global strategy whereas pigeons display a dominance of the left hemisphere. Thus, behavioral asymmetries are linked to a stronger bilateral input to the right hemisphere in chickens but to the left one in pigeons. The degree of bilateral visual input may determine the dominant visual processing strategy when redundant encoding is possible. This analysis supports that environmental stimulation affects the balance between hemispheric-specific processing by lateralized interactions of bottom-up and top-down systems.

Keywords: cerebral lateralization, visual system, hemispheric strategy, local-global analysis, social recognition, spatial orientation, avian

GENERAL CEREBRAL ASYMMETRIES IN VERTEBRATES

In contrast to original views, cerebral lateralization is a widespread phenomenon in the animal kingdom. Functional and structural differences between left and right brain sides are in no way exclusive for humans but can be found in other vertebrates and even in invertebrates (Vallortigara et al., 1999; Halpern et al., 2005; Vallortigara and Rogers, 2005; Corballis, 2009; Concha et al., 2012; Ocklenburg and Güntürkün, 2012). A widespread functional lateralization is for example the preferential limb use for specific tasks. In mammals, obviously humans show strong hand preferences (Corballis, 2009) but also chimpanzees (Hopkins et al., 2011), mice (Collins, 1975), bats (Zucca et al., 2010) and wallabies (Giljov et al., 2012) show significant side preferences when using their limbs. Furthermore, species of the avian and amphibian class like parrots (Brown and Magat, 2011), chickens (Rogers and Workman, 1993), and toads (Bisazza et al., 1996) show dominance for using one limb on a given task. Strength of lateralization and preferred side differ between species and are in some cases dependent on environmental factors (for an overview, see Ströckens et al., 2013a). Beside limb preference, conspecific vocalization (e.g., language in humans) seems to be broadly lateralized in vertebrates. Most humans show a dominance of the left hemisphere for the production and perception of language (Flöel et al., 2005; Bethmann et al., 2007). Hemispheric dominance for processing conspecific vocalization can also be found in chimpanzees (Taglialatela et al., 2008), sea lions (Böye et al., 2005), dogs (Siniscalchi et al., 2008), or Zebra, and Bengalese finches (Okanoya et al., 2001; Poirier et al., 2009). Interestingly, mammalian species show in all known cases dominance of the left hemisphere for conspecific vocalization while avian species vary in the predominantly used side (for review, see Ocklenburg et al., 2013a). In different species like humans, sheep, or chicken, the right hemisphere is dominant for aspects of social cognition (Brancucci et al., 2009; Corballis, 2009; Daisley et al., 2009; Rosa Salva et al., 2012) as well as spatial processing (Tommasi and Vallortigara, 2001; Vogel et al., 2003; Diekamp et al., 2005; Chiandetti, 2011).

Such hemispheric specializations might be related to differences in hemispheric processing style. Several authors have tried to classify general lateralization patterns and to associate them with hemispheric-specific processing strategies. According to these models, the left hemisphere prefers

a serial, or categorical processing style relying on local or high-frequency aspects of stimuli, while the right hemisphere favors parallel or configural processing, encoding global or low-frequency information (e.g., Dien, 2008). For instance, the left-hemispheric dominance for language processing may follow from a left-hemispheric advantage in encoding rapid frequency transitions (Tervaniemi and Hugdahl, 2003). There is evidence that a general dichotomy in encoding information is shared by different vertebrate species and hence, has an evolutionary origin (Vallortigara and Rogers, 2005; Yamazaki et al., 2007; Corballis, 2009; McGilchrist, 2010; Concha et al., 2012).

THE PUZZLE OF NATURE-NURTURE INTERACTIONS IN GENERATING A LATERALIZED BRAIN

Nevertheless, it is completely unclear how opposed encoding strategies are generated during ontogeny. Similarities between different species and the presence of an asymmetry pattern at the population level suggest a determination by genotypic factors. On the other hand, a high degree of plasticity indicates that envirotypic factors have a strong impact onto the mature lateralization pattern. Biased environmental stimulation, for example, affects hemispheric dominances and how the hemispheres interact to establish and maintain a lateralized functional organization for optimal cognition (Manns, 2006; Concha et al., 2012; Bishop, 2013; Hervé et al., 2013). Further envirotypic factors like hormones or cultural influences can also play a role in the formation of brain asymmetries (Laland, 2008; Schaafsma et al., 2009; Lust et al., 2011). Moreover, geno- and envirotypic effects may converge onto epigenetic processes, like DNA methylation, that ultimately determine lateralization patterns (Poole and Hobert, 2006; Hervé et al., 2013).

Functional asymmetries presumably rely on structural left-right differences in intra- and interhemispheric connectivity patterns (Ocklenburg and Güntürkün, 2012; Hervé et al., 2013; Ocklenburg et al., 2013b) that develop in a tight interplay between geno- and envirotypic factors. Principle differences in the mode of hemispheric-specific processing should be based on variances in the neuronal organization of the left and right brain sides. For example, differences in the neuronal organization of Brodmann area 22 predispose the left hemisphere for speech processing (Galuske et al., 2000). In the human brain, there are gross morphological asymmetries like a leftward asymmetry in planum temporale (for review, see Amunts, 2010) that appear very early during development (Chi et al., 1977). In right-handers, the planum temporale asymmetry is directly related to the left-hemispheric dominance for language processing. Accordingly, they may represent a suitable indicator of cerebral asymmetries. In sinistrals, however, this asymmetry is less pronounced (Geschwind et al., 2002; Foundas et al., 2002; Greve et al., 2013; Meyer et al., 2013). Moreover, pre- and postnatal events can affect asymmetry during development of the planum temporale and disrupt twin concordance (Steinmetz et al., 1995; Eckert et al., 2002). Dissociation between gross morphological and functional asymmetries suggests that they do not reflect left-right differences in the fine structure of neuronal circuits. Recent studies therefore underline the relevance of microstructural differences in human cortical hemispheres that range from dendritic tree features and neuronal cell size up to differences in white matter organization (Stephan et al., 2007; Ocklenburg et al., 2013b).

The microstructural organization of local networks, as well as their afferent and efferent connections, develops in close interactions with envirotypic factors. For more than 50 years, it is known that sensory experience is a critical factor for the activity-dependent fine tuning of neuronal systems (Hubel and Wiesel, 1959; Wong and Ghosh, 2002; West and Greenberg, 2011). Therefore, biased sensory experience can induce subtle differences between the neuronal organization of the left and right brain side, which in turn determine the mature functional lateralization pattern. A neuronal network that is better adjusted to specific processing may enable one hemisphere (a) to adopt dominance for a specific function, (b) to analyze stimuli according to a preferential processing strategy, or (c) to exert dominance in case of conflicts between the hemispheres. It is still under debate, which effects are critical for the establishment of a lateralized functional brain organization (e.g., Bloom and Hynd, 2005; Hervé et al., 2013).

A differentiation between these possibilities requires animal models, which allow modulations of the lateralization pattern by manipulating the action of specific envirotypic factors. The visual system of birds, like chickens or pigeons, is a well suited model for such kind of experiments. In both species, behavioral asymmetries can be associated with morphological left-right differences of the visual pathways at the individual as well as the population level. Critical aspects of these asymmetries depend on unbalanced light stimulation during development (e.g., Vallortigara and Rogers, 2005; Manns, 2006; Rogers et al., 2007; Güntürkün and Manns, 2010). This supports that lateralization is generated within the scope of ontogenetic plasticity and suggests causal relations between structural and functional asymmetries. Although at first glance quite similar, the two avian models display profound differences in the functional and structural outcome that is based on the asymmetrical visual experience. These differences shed light on the interrelations between structural and functional asymmetries that we want to discuss in the following sections. To this end, we start with a short description of avian visual lateralizations and their development followed by a deeper analysis of differences between chickens and pigeons.

THE LATERALIZED ORGANIZATION OF THE AVIAN VISUAL SYSTEM – A MODEL TO RESOLVE THE PUZZLE

The visual system of birds is lateralized with a pattern that is similar to humans. The left hemisphere dominates the discrimination of small optic details, rule learning, or categorization of visual stimuli. The right hemisphere on the contrary, is in charge of spatial attention and aspects of social cognition (Daisley et al., 2009; Manns and Güntürkün, 2009). These hemispheric specializations can be easily tested just by temporarily occluding one eye with an eye cap, i.e., by monocular testing, since the optic nerves cross virtually completely in birds. Accordingly, information from the left eye is primarily directed to the right brain side and vice versa.

Behavioral asymmetries are accompanied by anatomical left-right differences within the ascending visual pathways. In both,

pigeons and chickens, structural asymmetries are mainly represented by a difference in projection strength between the two hemispheres. This projection asymmetry corroborates the idea that differences in anatomical connectivity constitute the critical structural substrate of functional asymmetries between the hemispheres (Stephan et al., 2007). But in each species, different visual systems are affected (**Figure 1**). In pigeons, the tectofugal pathway (corresponding to the extrageniculate pathway in mammals) is lateralized, with soma size asymmetries of mesencephalic and diencephalic neurons indicating left-right differences in the complexity of their neuronal connections (Güntürkün, 1997; Manns and Güntürkün, 1999a, 2003; Freund et al., 2008). Moreover, projections of the right optic tectum to the contralateral nucleus rotundus are stronger than the projections of the left tectum to the right rotundus. Since the number of ipsilaterally ascending fibers does not differ between sides, the asymmetry of the contralateral projections effectively increases the total tectal input on the left rotundus (Güntürkün et al., 1998). Thus, it is the left hemisphere that receives a more complete representation of information from both visual hemifields (Valencia-Alfonso et al., 2009). The second major visual pathway aside from the tectofugal, the thalamofugal pathway (corresponding to the geniculo-cortical pathway in mammals), is not lateralized in pigeons, neither in young nor adult birds (Ströckens et al., 2013b). In chickens, however, the thalamofugal pathway but not the tectofugal one shows an asymmetry in its projection pattern whereas cell size asymmetries are not known. In the chickens' thalamofugal pathway, the left nucleus geniculatus lateralis pars dorsalis (GLd) comprises more projections to right telencephalic visual Wulst than the right GLd to the left visual Wulst. As the ipsilateral GLd-Wulst projections are symmetric between sides, the contralateral projection asymmetry leads to a higher total GLd input on the right visual Wulst (Rogers and Bolden, 1991; Rogers and Deng, 1999). In contrast to the stable tectofugal asymmetries in pigeons (Güntürkün et al., 1998), the lateralization of the chicken's thalamofugal system only persists for three weeks after hatch (Rogers and Sink, 1988).

LIGHT-DEPENDENT DEVELOPMENT OF VISUAL ASYMMETRIES

The envirotypic factor light plays an important role for the induction and stabilization of a subset of visual asymmetries in pigeons and chickens. Avian embryos take an asymmetrical position inside the egg, with the right eye pointing towards the semitransparent eggshell. The left eye, however, is occluded by the embryos body (Kuo, 1932). This positioning leads to a stronger light stimulation of the right in comparison to the left eye, which triggers lateralization processes on the anatomical as well as the functional level. In pigeons, this causes an asymmetry in the projections of the tectofugal pathway (Güntürkün et al., 1998) while in chickens projections of the thalamofugal pathway are affected (Rogers and Bolden, 1991; Rogers and Deng, 1999; Koshiba et al., 2003). Dark incubation of eggs prevents establishment of several asymmetries (Rogers and Sink, 1988; Skiba et al., 2002; Manns and Güntürkün, 2003; Freund et al., 2008) and impairs interhemispheric cooperation (Manns and Römling, 2012). Furthermore, in the altricial pigeon, monocular light deprivation during a short plastic period after hatch can strengthen or even alter the direction of visual asymmetries (Manns and Güntürkün, 1999a,b).

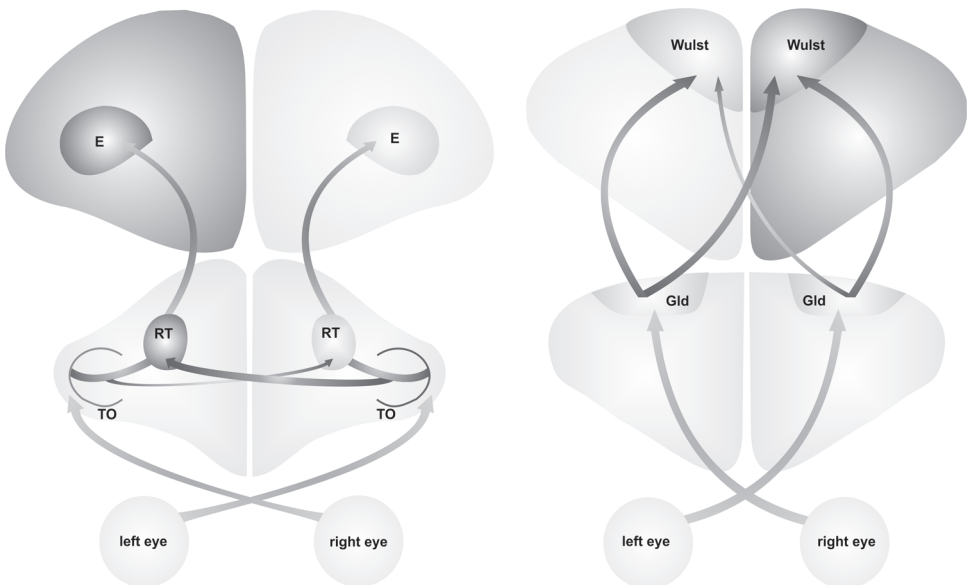


FIGURE 1 | Visual processing in the tectofugal pathway of pigeons (left side) and the thalamofugal pathway of juvenile chickens (right side) is asymmetrically organized. In pigeons the projection from the right tectum opticum (TO) to the left nucleus rotundus (RT) are stronger than projection from the right TO to the left RT. In chickens the contralateral projections from left nucleus geniculatus lateralis pars dorsalis (Gld) to the right visual Wulst are stronger than projections from the right Gld to the left visual Wulst. These projection asymmetries lead to higher bilateral input to the left hemisphere in pigeons and to the right hemisphere in pigeons (indicated by darker coloring). These anatomical asymmetries lead to a lateralized behavior in each species (E, entopallium).

In sum, pigeons and chickens develop behavioral as well as anatomical asymmetries depending on the ontogenetic light conditions. But the characteristics of the structural lateralizations differ in at least three major aspects between the two species: (1) the affected pathway (tectofugal in pigeons versus thalamofugal in chickens), (2) the constancy of the lateralization (persistent in pigeons versus transient in chickens), and (3) the hemisphere, which receives stronger bilateral input (left in pigeons versus right in chickens). These differences allow speculating about the causal relations between light-dependent structural and behavioral asymmetries. A closer look at the functional asymmetry pattern of chickens and pigeons suggests that the action of light is more complex as indicated at first glance. Asymmetrical photic stimulation modifies the lateralized interaction of bottom-up and top-down systems that ultimately determine lateralized functional processing.

INTERRELATIONS BETWEEN LIGHT-DEPENDENT STRUCTURE AND FUNCTION

Enhancement of fine-tuned visuomotor circuits within the left hemisphere

Especially left-hemispheric specializations of chickens and pigeons are remarkably similar. Although the behavioral paradigms testing hemispheric asymmetries differ in detail, experiments demonstrate left-hemispheric advantages for visuomotor control that are similar to human left frontal dominances for response inhibition (e.g., Weisbrod et al., 2000; Warren et al., 2013), action planning (Serrien and Sovijärvi-Spapé, 2013), and categorization (e.g., Parrot et al., 1999). The left hemisphere is in charge of the selection of features allowing stimuli to be assigned to discrete categories when discriminating food objects (Mench and Andrew, 1986; Güntürkün and Kesch, 1987; Vallortigara et al., 1996; Rogers, 1997; Rogers et al., 2007) or abstract concepts like humans or painting styles (reviewed in Yamazaki et al., 2007). In pigeons, the superior visual discrimination abilities are related to better left-hemispheric memory capacities when pigeons are required to memorize large numbers of abstract pattern (von Fersen and Güntürkün, 1990) or when they have to perform an object-specific working memory task (Prior and Güntürkün, 2001). Even though the left hemisphere of the chicken brain is not better in using object specific cues in a working memory task (Regolin et al., 2005), it is critically involved in specific forms of quick memory formation like passive avoidance learning (Sandi et al., 1993). In chickens and pigeons, the left hemisphere controls pecking, enabling faster and more accurate responses (Güntürkün, 1985; Güntürkün and Kesch, 1987; Skiba et al., 2002) or inhibiting inappropriate responses (Deng and Rogers, 1997; Rogers et al., 2007).

At least some of the described left-hemispheric dominances emerge in response to asymmetrical photic stimulation during ontogeny. It is well known that sensory experiences have a significant influence over the way the brain is assembled and thus, can functionally impact the way the mature brain works (West and Greenberg, 2011). Transiently enhanced visual input triggers activity-dependent differentiation processes (Manns et al., 2005, 2008; Manns and Güntürkün, 2009; Güntürkün and Manns, 2010) resulting in better fine-tuned visuomotor circuits as demonstrated in numerous plasticity studies (for review e.g., Wong and Ghosh, 2002; Berardi et al., 2003; Espinosa and Stryker, 2012). As a consequence, the left hemisphere of birds is better adjusted to adopt specific visuomotor functions and hence, takes over control. Pre- and posthatch modulations of lateralized visual experience support that the hemisphere that is more strongly activated by light develops a functional dominance (Rogers and Sink, 1988; Manns and Güntürkün, 1999a; Prior et al., 2004a).

Since the emergence of behavioral asymmetries are accompanied by structural left-right differences within the ascending visual pathways (Deng and Rogers, 2000; Manns and Güntürkün, 2009) it is conceivable that they are causally related. A causal relationship would support models proposing that connectivity asymmetries between the hemispheres are critical for cerebral lateralizations since they impact differences in computational principles used by the left and right brain side, which determine their functional properties (Stephan et al., 2007). It is obvious that light input primarily affects the development of ascending visual pathways (Manns and Güntürkün, 2009; Güntürkün and Manns, 2010). Asymmetrical activity-dependent neuronal processes mediate lateralized differentiation of visual neurons leading to asymmetrical neuronal properties that represent the structural correlate of functional lateralizations. In parallel, the ascending systems develop intrinsic functional asymmetries mediating lateralized bottom-up processing (Manns and Güntürkün, 2009; Güntürkün and Manns, 2010). Electrophysiological studies in pigeons have demonstrated more left- than right-rotundal neurons, which respond to contra- as well as ipsilateral visual input (Folta et al., 2004). This is in accordance to the stronger bilateral tectal innervation. Left entopallial neurons are more responsive to visual stimulation and after associative learning they show a higher degree of differentiation between the rewarded and the unrewarded stimulus (Verhaal et al., 2012).

Despite the presence of structural as well as physiological asymmetries in the ascending pathways, the left-hemispheric dominance for visuomotor control cannot simply be based on stronger bottom-up input. A first hint is given by the fact that the visual pathways that show anatomical asymmetries differ between pigeons and chickens (**Figure 1**). Although left-hemispheric development is enhanced in the pigeons' tectofugal as well as the chickens' thalamofugal system, stronger bilateral input is guided to the left hemisphere in pigeons but to the right one in chickens. Moreover, only the tectofugal projection asymmetries in pigeons are stable (Güntürkün et al., 1998; Rogers and Deng, 1999) whereas thalamofugal asymmetries in chickens are transient (Deng and Rogers, 2002). Nevertheless, some left hemispheric dominances in hens remain even when projection asymmetries are lost (McKenzie et al., 1998).

This discrepancy can be explained by the critical role of top-down systems onto lateralized visuomotor behavior. Top-down influences arise from the forebrain and exert asymmetrical impact onto visual processing by efferents descending towards the brainstem. Here, they converge onto commissural systems, which regulate lateralization of visuomotor responses in pigeons (Güntürkün and Böhringer, 1987) and chickens (Parsons and Rogers, 1993) and which might be involved in the efficiency of

interhemispheric cooperation (Manns and Römling, 2012; Letzner et al., 2014). One source of top-down influences is the hyperpallium or visual Wulst that represents on the one hand the telencephalic target of the thalamofugal pathway (**Figure 1**) but on the other hand a multimodal area reciprocally connected with several telencephalic nuclei (Reiner and Karten, 1983; Shimizu et al., 1995; Deng and Rogers, 2000, cited in Manns et al., 2007). Accordingly, the Wulst is not only a visual structure, but is also involved in higher cognitive functions, playing a role in learning and attentional processes (reviewed in Manns and Güntürkün, 2009). Several studies in pigeons as well as chickens show that the left Wulst exerts a stronger impact onto visuomotor behavior than the right one (Manns and Güntürkün, 2009; Valencia-Alfonso et al., 2009). In pigeons, transient silencing of hyperpallial activity by injections of the sodium channel blocker tetrodotoxin demonstrates that the left Wulst controls tectofugal processing (Folta et al., 2004), modulates access to transfer information (Valencia-Alfonso et al., 2009), and controls motor response in case of conflicting information (Freund et al., 2009.). In chickens, disturbance of neurotransmission by manipulating amino acid pools with telencephalic injections of cycloheximide or glutamate demonstrates that the left hemisphere exerts better inhibitory control on visuomotor behavior than the right one. Only injections into the left but not the right Wulst increase inappropriate pecks onto pebbles in the pebble-grain discrimination task and elevate aggressive and sexual behavior (Rogers and Anson, 1979; Howard et al., 1980; Bullock and Rogers, 1986; Deng and Rogers, 1997, 2002).

It is intriguing that at least some aspects of hyperpallial top-down influences depend on asymmetrical visual experience during embryonic development. Hyperpallial control of categorizing grains as different from pebbles in chickens only emerges in light-stimulated chickens. In dark-incubated birds, treatment of neither the left nor the right Wulst affected performance on the pebble-grain task (Deng and Rogers, 2002). In pigeons, an endogenously present right-hemispheric superiority in accessing visual transfer information is reversed by embryonic light stimulation and it is likely that this effect results from modulations of top-down systems (Letzner et al., 2014).

Although the Wulst represents the telencephalic target of the thalamofugal projection, it is unlikely that the lateralized action of the Wulst depends on structural thalamofugal asymmetries. In pigeons, no thalamofugal projection asymmetries are present at all (Ströckens et al., 2013b). Even in chicks there is dissociation between the development of thalamofugal and behavioral asymmetries. The left-hemispheric dominance in categorizing grains from pebbles depends on the wavelength of the stimulating light and hence, depends on color-coding pathways outside the thalamofugal system. In contrast, thalamofugal projection asymmetries develop independent from wavelength characteristics of the photic stimulus (Rogers and Krebs, 1996).

In sum, we speculate that the emergence of a left-hemispheric dominance in visuomotor control is caused by a transient ontogenetic light trigger independent from the generation of projection asymmetries within ascending visual pathways. A decisive factor is rather the development of lateralized top-down systems. This does not mean that asymmetrical bottom-up projections do not influence lateralized functional processing. In the next paragraph, we will discuss in how far the degree of bilateral ascending input may affect preferential processing strategies and hence, hemispheric dominance in cases of redundant or conflict encoding.

Hemispheric-specific processing strategies in analyzing visual stimuli

In principle, environmental stimuli can be analyzed according to different strategies. One is based on a detailed feature analysis attending to local cues. The other one uses global information considering relational cues between stimulus aspects. In principle, both hemispheres can process local as well as global information depending on context and/or -inner states. Nevertheless, several studies in chickens and pigeons demonstrate that the hemispheres differ in their preferential strategies whereby the left hemisphere prefers local, the right one global encoding (Vallortigara and Rogers, 2005; Yamazaki et al., 2007). A conflict can arise when local and global cues provide contradictory information and hence, suggest different response options. In these situations, neuronal mechanisms are required to coordinate a common decision. In many cases, one hemisphere dominates processing and/or behavioral response (Levy and Trevarthen, 1976). Some evidences suggest that pigeons and chickens differ in the dominance pattern for specific functions. Chickens seem to rely more on a right-hemispheric strategy depending on global cues whereas it is the left hemispheres in pigeons that dominates visual processing thereby preferentially encoding local cues (Vallortigara and Rogers, 2005; Daisley et al., 2009; Shimizu et al., 2010; Rosa Salva et al., 2012; Tommasi et al., 2012). A closer look however, indicates that there is some dissociation between hemispheric dominance and processing strategy. This suggests that it is not only an evolutionary based dichotomy in processing style that determines a preferential strategy in analyzing complex visual stimuli. Instead, the lateralized organization of the visual systems may also play a prominent role (Tommasi et al., 2012). We propose that the degree of bilateral input affects the dominant hemisphere and encoding strategy, which are affected by the ontogenetic light conditions in a species-dependent manner.

A first hint comes from social recognition, a cognitive function that is generally assumed to be dominated by right-hemispheric processing (Corballis, 2009; Daisley et al., 2009; Rosa Salva et al., 2012). For example, chicks recognize individual companions and choose to approach cage mates in preference to unfamiliar ones only when using their left eye (Deng and Rogers, 2002). This right-hemispheric dominance is related to the preferential right-hemispheric attention to global feature cues that are used to select mates, identify rivals, locate young, and differentiate members of higher and lower ranks (Rosa Salva et al., 2012). In contrast, pigeons attend to local facial features rather than their configuration when they are required to discriminate between intact faces of conspecifics and globally altered ones in which local features are spatially rearranged (Patton et al., 2010; Shimizu et al., 2010). This strategy fits to a general preference to analyze local elements of visual stimuli and to a general left-hemispheric dominance for categorization (Cavoto

and Cook, 2001; Yamazaki et al., 2007; Shimizu et al., 2010). It is not directly tested yet if the preferential encoding of object details is actually related to a left-hemispheric dominance. Verification would indicate a converse dominance pattern for aspects of social recognition in chickens and pigeons that is in correspondence to the hemisphere that receives stronger bilateral visual input.

A second hint is provided by detailed analysis of spatial orientation tasks that indicates dissociation between hemispheric specializations and strategy. Comparable to social recognition, spatial orientation is generally described as a right-hemispheric domain. Accordingly, chickens as well as pigeons place more pecks on objects located within the left visual field indicating a functional dominance of the right hemisphere for visuo-spatial attention comparable to humans (Diekamp et al., 2005; Chiandetti, 2011). But for spatial functions like localization of the own position in space, for orientation, and navigation, more complex spatial processing is required using local, non-geometric as well as global, geometric information about the environment. Several experiments demonstrate that both hemispheres are basically able to encode geometric as well as non-geometric information in natural and semi-natural settings. Nevertheless, orientation behavior under different seeing conditions suggest hemispheric-specific differences in using geometric (global) or non-geometric (local) strategies (Vallortigara and Rogers, 2005; Tommasi et al., 2012). Again, there are evidences for a differential lateralization pattern between chickens and pigeons that mainly arise when spatial cues provide conflicting information.

In a classical study, Tommasi and Vallortigara (2001) trained chicks to locate food buried under sawdust in the center of a square arena providing geometric and/or non-geometric landmark cues. In a conflict situation when landmarks and geometry of the arena point to different localization of food, chicks seeing with the right eye rely on the landmark cues, whereas they consider the geometric information when seeing with the left eye. Thus, chickens demonstrate a clear difference between left- and right-hemispheric search strategies. Moreover, performance under binocular seeing conditions does not differ from the one when seeing with the left eye. This indicates that the right-hemispheric geometric strategy dominates visuospatial orientation (Tommasi and Vallortigara, 2001). Unilateral hippocampal lesions confirmed this pattern (Tommasi et al., 2003). A completely different pattern was detected in pigeons that were trained in a very similar task (Wilzeck et al., 2009). Although monocular tests confirm that each brain hemisphere consider geometric as well as landmark information, both hemispheres encode landmark information more heavily than geometric one in conflict situations. Only when using both eyes, pigeons rely preferentially on geometric cues. Thus, in contrast to chickens, pigeons do not demonstrate an asymmetry in monocular search strategy; they rather display a preferential use of a local encoding strategy that is not bound to one hemisphere.

A similar species difference in hemispheric-specific contributions to search strategies could be detected in spatial working memory tasks combining object- and position-specific information. Chicks show a right-hemispheric dominance for locating a target on the basis of position-dependent cues but participation of both hemispheres is required for locating a target on the basis of object-specific cues. When object and positional cues provide contradictory information, the right hemisphere preferentially attends to position-specific, geometric cues, whereas the left hemisphere tends to attend to object-specific features. When seeing with both eyes, chickens attend to geometric cues supporting the dominance of the right-hemispheric strategy (Regolin et al., 2005). A similar working memory task with pigeons shows that the left hemisphere is dominant in processing object-specific/local information while both hemispheres encode global geometric information to an equal degree (Prior and Güntürkün, 2001). Thus, in contrast to chicken, the left hemisphere of pigeons is not only specialized for local visual analysis but also attends to global features. This is supported by hippocampal lesion studies demonstrating that the left hippocampus is critically involved in the representation of a goal when geometric encoding is required (Nardi and Bingman, 2007). Accordingly, the left hemisphere plays generally a more important role in natural homing behavior (Ulrich et al., 1999; Prior et al., 2004b).

In sum, spatial reference and working memory tasks demonstrate a clearly lateralized use of spatial information in chickens: the left hemisphere encodes local non-geometric information and the right one relies on global, geometric cues. This pattern supports an evolutionary conserved dichotomy. Moreover, preferential encoding of geometric information under binocular seeing conditions demonstrates the dominance of the right-hemispheric global strategy. In pigeons, however, there is evidence for a dominance of the left hemisphere in spatial orientation tasks whereby it does not only use local but also global cues. An explanation for this differential pattern might be related to the differential organization of the ascending visual pathways. The right-hemispheric dominance in chickens is in accordance with the stronger bilateral input and hence, right-hemispheric activation even under binocular seeing conditions. In contrast, the stronger innervation of the left hemisphere in pigeons leads to enhanced left-hemispheric activation. Accordingly, even when seeing with the left eye, the left hemisphere is strongly activated and dominates visual analysis as indicated by the preferential encoding of local feature cues. On the other hand, since the left hemisphere is also able to encode global information, suitable tasks demonstrate a left-hemispheric dominance independent from available visual cues. Dominance may result from a more complete representation and/or simply enhanced hemispheric activation due to a stronger bilateral input. The contribution of different visual pathways indicate some species-dependent differences; but since the degree of bilateral input to the hemispheres is controlled by the ontogenetic light conditions, the differential hemispheric-specific encoding pattern further supports the critical role of environmental factors.

CONCLUSION: SIMILAR BUT DIFFERENT – HOW ONE ENVIROTYPIC FACTOR AFFECTS THE INTERACTION OF BOTTOM-UP AND TOP-DOWN SYSTEMS

A close comparison of the two most intensively studied avian models – chickens and pigeons- sheds light onto three aspects of cerebral lateralization: (1) it exemplifies the critical impact of an

envirotypic factor for the generation of a lateralized neuronal system whose action is superimposed on endogenous asymmetries. (2) It indicates dissociation between structural and functional asymmetries that are (3) related to an intimate interaction of bottom-up and top-down systems in a species-dependent manner – an interaction that is much more complex than originally assumed (e.g., Gilbert and Li, 2013).

In chickens as well as pigeons, asymmetrical visual light experience during embryonic development leads to structural and functional lateralizations of their visual systems. A left-hemispheric dominance in visuomotor control is induced by shortly enhanced photic stimulation and is accompanied by the emergence of projection asymmetries in the ascending pathways. Which visual pathway develops structural asymmetries seems to depend on species-dependent differences in the ontogenetic susceptibility to light stimulation (Ströckens et al., 2013b); however, they are not a prerequisite for the generation of hemispheric dominance.

Ultimate consequences of biased visual experience may be established at forebrain level from where lateralized top-down systems control visual processing. Top-down asymmetries develop as secondary consequences of asymmetrical visual stimulation, presumably during posthatch stabilization of induced asymmetries involving negative feedback loops, which preserve asymmetries even in the absence of lateralized input (Manns, 2006; Manns and Güntürkün, 2009). Thereby they may differentiate own microstructural asymmetries but, known as up to now, no asymmetries in efferent projections (Manns et al., 2007). Once established, higher lateralized (top-down) systems are not necessarily longer dependent on asymmetrical bottom-up input. They can exert their action on visual processing presumably by mesencephalic commissural systems onto which ascending and descending visual pathways converge (Manns and Güntürkün, 2009; Güntürkün and Manns, 2010). In turn, these commissural systems regulate lateralization of visuomotor control in pigeons (Güntürkün and Böhringer, 1987) and chickens (Parsons and Rogers, 1993) and might be involved in the efficiency of interhemispheric cooperation (Manns and Römling, 2012; Letzner et al., 2014).

This critical impact of lateralized top-down processes in no way means, that stable bottom-up asymmetries do not affect hemispheric dominances. On the one hand, asymmetrical projections may result in asymmetrical salience of stimuli represented within the left and right hemisphere eventually triggering different processing strategies. On the other hand, asymmetrical innervation may cause enhanced activation of the hemisphere that receives stronger bottom-up input. As a consequence, this hemisphere is quicker in response generation or may recruit more attentional resources and hence, dominates visuomotor processing as a result of a "horse race" between the hemispheres (e.g., Corballis, 1998). This idea is supported by hints for left-hemispheric metacontrol in pigeons (Adam and Güntürkün, 2009; Freund et al., 2009). The absence of similar metacontrol in chickens would suggest that permanent asymmetrical bottom-up systems are critical for hemispheric dominances.

The critical role of lateralized bottom-up systems as indicated by the degree of bilateral ascending projections may also tackle another basic aspect of hemispheric-specific processing. It is intriguing that although left-hemispheric development is enhanced in the pigeons' tectofugal as well as the chicken's thalamofugal system, stronger bilateral input is guided to the left hemisphere in pigeons but to the right one in chickens. This may lead to a differential degree of activation and may influence the balance of left- and right-hemispheric processing. Although both hemispheres can encode local as well as global feature cues, the hemispheres differ in their preferential encoding strategies. This lateralization seems to have some phylogenetic foundation (Vallortigara and Rogers, 2005; McGilchrist, 2010; Concha et al., 2012) but might be affected by ontogenetic experiences. Comparing the lateralization patterns of pigeons and chickens, we propose that the degree of bilateral visual input influences the use of encoding strategies, which therefore depends on asymmetrical photic stimulation. This hypothesis still has to be tested in animals with different ontogenetic light experiences. These studies will provide important clues for a deeper understanding of the experience-dependent interplay between bottom-up and top-down processing that are superimposed by species-dependent endogenous asymmetries.

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Lateralized mechanisms for encoding of object. Behavioral evidence from an animal model: the domestic chick (*Gallus gallus*)

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In our previous research we reported a leftward-asymmetry in domestic chicks required to identify a target element, on the basis of its ordinal position, in a series of identical elements. Here we re-coded behavioral data collected in previous studies from chicks tested in a task involving a different kind of numerical ability, to study lateralization in dealing with an arithmetic task. Chicks were reared with a set of identical objects representing artificial social companions. On day 4, chicks underwent a free-choice test in which two sets, each composed of a different number of identical objects (5 vs.10 or 6 vs. 9, Experiment 1), were hidden behind two opaque screens placed in front of the chick, one on the left and one on the right side. Objects disappeared, one by one, behind either screen, so that, for example, one screen occluded 5 objects and the other 10 objects. The left-right position of the larger set was counterbalanced between trials. Results show that chicks, in the attempt to rejoin the set with the higher number of social companions, performed better when this was located to the right. However, when the number of elements in the two sets was identical (2 vs. 2, in Experiment 2) and they differed only in the coloration of the objects, this bias was not observed, suggesting a predisposition to map the numerical magnitude from left to right. Future studies should be devoted to the direct investigation of this phenomenon, possibly employing an identical number of mono-chromatic imprinting stimuli in both conditions involving a numerical discrimination and conditions not involving any numerosity difference.

Keywords: number cognition, lateralization, counting, number sense, arithmetic, addition, subtraction, domestic chick

INTRODUCTION

Since Aristotle argued that "logos" is the essence of the human mind, logic and language were considered strictly connected (Houndé and Tzourio-Mazoyer, 2003; Vallortigara et al., 2010a,b; Vallortigara, 2012). From this perspective, all cognitive abilities, and especially mathematical thinking, were believed to be firmly related to language. This is likely to be correct for symbolic mathematical capacity (Carey, 2004). Indeed, the ability to represent number and selected numerical concepts, such as real numbers, logarithms, and square roots, is only performed by a subset of human beings, who have received specific mathematical education. Nonetheless, human adults are also able to master some numerical tasks when, under specific experimental conditions, language use is prevented (Cordes et al., 2001). This non-verbal "number sense" (all those calculations that could be solved in the absence of numerical words) can be found, for example, in tasks requiring individuals to add two sets of dots presented sequentially and to choose between a correct and an incorrect alternative. In this kind of task, both college students and rhesus monkeys (*Macaca mulatta*) are quicker and more accurate at selecting the greater of two numbers when the numerical distance between them is larger than when it is smaller (this is referred to as the Distance Effect). They also perform better in distinguishing between two small numbers compared to two larger numbers when the numerical distance is equal (this is referred to as the Magnitude Effect). Such a similarity in performance suggests that humans share a numerical processing mechanism with other animal species (Cantlon and Brannon, 2007).

Although this is the most direct evidence of an ancestral numerical mechanism shared by humans and non-humans, other supporting data have been obtained from non-human creatures (reviews in Vallortigara et al., 2010a,b). Rhesus monkeys (*Macaca mulatta*; Brannon and Terrace, 1998; Merritt et al., 2009), hamadryas baboons (*Papio hamadryas*), squirrel monkeys (*Saimiri sciureus;* Smith et al., 2003) and brown capuchin monkeys (*Cebus apella;* Judge et al., 2005) were able to master numerical tasks involving numbers up to 9, showing that discrimination of a numerical comparison depends on the ratio of the to be discriminated numbers (see also Call, 2000; Call, for evidence of numerical competence in orangutangs, *Pongo pygmaeus*). Some studies have shown that numerical cognition is not just a prerogative of primates, but that it can be found also in a non-mammalian species, for example in the Class Aves. Simple quantity discrimination (preference for the bigger between two

sets of food items) has been demonstrated in robins (*Petroica longipes*) (Garland et al., 2012). An African gray parrot (*Psittacus erithacus*) even learned to use labels to order numbers up to 8 (Pepperberg, 2012).

Evidence of number discrimination ability has been obtained also in very young birds (Rugani et al., 2008). Newborn chicks (*Gallus gallus*) were reared with two stimuli, each characterized by a different number of elements. Food was found in proximity of one of the two stimuli. Subjects were then tested with stimuli depicting novel elements representing either the numerosity associated or not associated with food. Chicks approached the number associated with food in the 2 vs. 3, 2 vs. 8, 6 vs. 9, 8 vs. 14, 4 vs. 6, and 4 vs. 8, 5 vs. 10, and 10 vs. 20 comparisons, and did so even when quantitative cues were unavailable or controlled (Rugani et al., 2013a). Spontaneous number discrimination was demonstrated also by taking advantage of chicks' sensitivity toward the fine visual characteristics of their own imprinting object. Chicks reared with groups of artificial stimuli of different numerousness prefer to approach, during a subsequent test, the set containing the higher number of imprinting objects in the comparisons 1 vs. 2, 1 vs. 3, and 2 vs. 3 (Rugani et al., 2010a). Moreover, when chicks are presented with sets of 2 vs. 3, 1 vs. 4, and 2 vs. 4 imprinting objects disappearing one-by-one, each set behind one of two screens, they spontaneously inspected the screen occluding the larger set, even when the continuous variables (total surface area or contour length) were controlled for (Rugani et al., 2009, 2013b,c). Nevertheless, when chicks were presented with comparisons between large numbers of objects (5 vs. 10 or 6 vs. 9), they succeeded only if non-numerical and numerical cues were both available (Rugani et al., 2011a).

From these and other evidence (see Vallortigara et al., 2010a,b for a review) it seems that numerical competence did not emerge *de novo* in linguistic humans, but has been likely built on precursor systems also available in non-human animals (Dehaene, 1997; Carey, 2009).

In the field of numerical cognition, another prerogative that, up to now, was considered to be uniquely human is the tendency to orient numbers from left (small numerical values) to right (large numerical values; Galton, 1880; Dehaene, 1993; Fias and Fischer, 2005; Bueti and Walsh, 2009). An example of this is provided by the SNARC (Spatial Numerical Association of Response Codes) effect, in which humans respond faster to smaller numbers with the left hand and to larger numbers with the right hand (Dehaene et al., 1993). Also, when adult humans attempted to generate numbers at random they were influenced by lateral head turns: when the participants were facing left they produced relatively small numbers, whereas when facing right they tended to produce larger numbers (Loetscher et al., 2008). Patients with left-sided visuospatial neglect, typically due to damage to the right parietal lobe, bisected the numerical interval with a systematic bias toward larger numbers (Zorzi et al., 2002). In addition to that, evidence supports a universal left-sided attention bias in number space: healthy subjects required to estimate the midpoint of a numerical interval show a systematic error, consistently misplacing the midpoint slightly to the left of its actual position (Göbel et al., 2001).

Many studies suggested that these lateralization effects emerge as a result of exposure to formal instruction (Shaki et al., 2009), since scholar education could reduce or even reverse the SNARC effect in cultures that read from right to left (Zebian, 2005; Shaki and Fischer, 2008; Shaki et al., 2009). However, the origins of this asymmetry, and particularly the degree to which it depends upon cultural experience, remains elusive. Recently de Hevia et al. (2008), de Hevia and Spelke (2010) have demonstrated that a predisposition to relate number to space develops early in life, before the acquisition of language. They have showed that 8-month-old infants transfer the discrimination of an ordered series of numerosities to the discrimination of an ordered series of line lengths. Infants therefore have an intrinsic preference for numbers and lengths that are positively related. Even more suggestive are the data that illustrate a tendency to represent numerical magnitudes as oriented from left to right in non-human animals (Rugani et al., 2007, 2010b, 2011b). Two bird species, domestic chickens and Clark's nutcrackers (*Nucifraga Columbiana*) were trained to select a target element in a series of identical ones, sagittaly oriented with respect to the bird's starting point. Birds were then tested with a series, identical to the first one, but rotated by 90°, so that the target could be identified either from the left or from the right end of the series. Both species selected the target with respect to the left end, suggesting that a disposition to map the numerical magnitude from left to right may originate from a prelinguistic precursor. Nevertheless, the leftward preference could be related to a general bias in the allocation of attention. In humans this phenomenon has been named "pseudoneglect" and reflects the fact that we primarily attend to the objects in the left side of space (Bowers and Heilman, 1980; Jewell and McCourt, 2000). Again, this is not a prerogative of human beings, in fact a selective allocation of attention to the left hemifield can be found also in birds during free foraging (Diekamp et al., 2005; Chiandetti, 2011) and in a comparative version of the line bisection task (Regolin, 2006). Somewhat similar phenomena favoring the left hemifield have been described also for amphibians (Vallortigara et al., 1998; Vallortigara and Rogers, 2005), suggesting a common mechanism shared by phylogenetically distant species.

Differently, an advantage for processing bigger numerosity, presented in the right hemispace, could not be explained as by product of selective left-sided attentional bias. In one of our studies, newly-hatched domestic chicks were reared for 3 days with a group of identical artificial imprinting objects. At test when animals were presented with sets of 5 vs. 10 (or 6 vs. 9) objects disappearing behind one of two identical screens, they spontaneously inspected the screen occluding the larger set (Rugani et al., 2011a). Across subsequent trials the larger set was made to disappear either behind the screen located to the left or to the right (with respect to the bird's starting position), offering the possibility to test for the presence of lateralization effects. Here we reanalyze the behavior of the subjects, to investigate if the performance is affected by the left-right position of the two sets. If a tendency to represent numerousness from left to right does exist in this species, we would expect an advantage when searching for the larger number of social companions if this is located to the right side.

EXPERIMENT 1

In previous studies we reported, in two bird species, a preference to map numbers from left to right, suggesting a lateralized representation of number space (Rugani et al., 2007, 2010a, 2011a,b).

Here we investigate this phenomenon by observing chicks' choice between a larger vs. a smaller group of artificial social companions (i.e., objects chicks have been familiarized to through exposure). Chicks are motivated to reach the larger group of objects. If smaller vs. larger numerosities are spatially mapped from left to right then we should expect chicks to be better at responding to the larger group when located on the right. Notably, such a finding would not be explained by the hypothesis of attentional facilitation for the left hemispace.

MATERIALS AND METHODS

Subjects and rearing conditions

For the present experiment we re-coded behavioral data from a sample of 36 female domestic chicks (*Gallus gallus*). Being the attractor a social stimulus we employed solely female chicks, since female chicks are more motivated than males to retrieve a social companion (Regolin et al., 2005). Data were originally collected by Rugani et al. (2011a). Subjects were obtained from a local commercial hatchery (Agricola Berica, Montegalda, Vicenza, Italy) when they were only a few hours old. On arrival at the laboratory, each chick was singly housed in standard metal home cage (28 cm wide × 32 cm long × 40 cm high) at controlled temperature (28–31°C) and humidity (68%), with food and water available *ad libitum* in transparent glass jars (5 cm in diameter, 5 cm high) placed at corners of the home cage. The cages were constantly (24 h/day) lit by fluorescent lamps (36 W), located 45 cm above the floor of the cages. Each chick was reared together with an imprinting stimulus composed of five identical objects. These were the same for all chicks and consisted of two-dimensional, about 1 mm thick, red plastic squares (2.5 × 2.5 cm). Each object was suspended in the center of the cage by a fine thread, at about 4–5 cm from the floor, so that they were all located at about chicks' head height.

Previous studies have shown that this kind of object is very effective in producing social attachment through filial imprinting in chicks (Rugani et al., 2009, 2010a, 2011a, 2013b).

Chicks were reared in these conditions from the morning (11 am.) of the 1st day to the morning (12 am.) of the 3rd day of life, when each subject singly underwent training and, about 2 h later, testing. In the time between training and testing, chicks were placed back to their own cage with their imprinting objects.

At test, different numerical comparisons were used for different groups of chicks. Eighteen chicks underwent the 5 vs. 10 comparison. These chicks were divided in two experimental groups, depending on the stimuli employed during testing. For the "no-control group" ($N = 10$), the original dimensions of the imprinting squares (2.5 × 2.5 cm) were maintained, so that both sets were composed of identical squares. In the "controlled-stimuli group" ($N = 8$), the set of 10 elements again comprised squares which dimensions were identical to those used during imprinting. On the contrary, the set of five elements comprised larger sized squares, balanced for either the overall area or for the overall perimeter. In fact, for half of the chicks of the "controlled-stimuli group" the dimensions of each square in the set of five elements were computed in order to match the overall perimeter of the set of 10 elements (with squares measuring 5.00 × 5.00 cm each). For the other 4 chicks, the set of five elements had the same overall area of the set of 10 elements (with squares measuring 3.54 × 3.54 cm each).

Other 18 chicks were tested with the comparison 6 vs. 9. As for the first numerical comparison, 10 chicks were tested with stimuli in which continuous variables co-varied along with numerousness. For this "no-control group," 15 identical squares measuring 2.5 × 2.5 cm were used. Again, the remaining eight chicks were tested with stimuli in which continuous variables were equated between the two sets. For half of the chicks of the "controlled-stimuli group" the dimensions of the squares in the set of six objects were computed to equate the overall perimeter of the set of nine objects (with squares measuring 3.75 × 3.75 cm each). The other 4 chicks were presented with sets equated in the overall area (with squares measuring 3.06 × 3.06 cm each).

Apparatus

Training and testing took place in an experimental room located near the rearing room. In the experimental room temperature and humidity were controlled (respectively, at 25°C and 70%). The room was kept dark, except for the light coming from a 40 W lamp, placed about 80 cm above the floor of the apparatus. The experimental apparatus (**Figure 1**) consisted of a circular arena (95 cm in diameter and 30 cm outer wall height) with the floor uniformly covered by a white plastic sheet. Within the arena, adjacent to the outer wall, was a holding box (10 × 20 × 20 cm), in which each subject was confined shortly before the beginning of

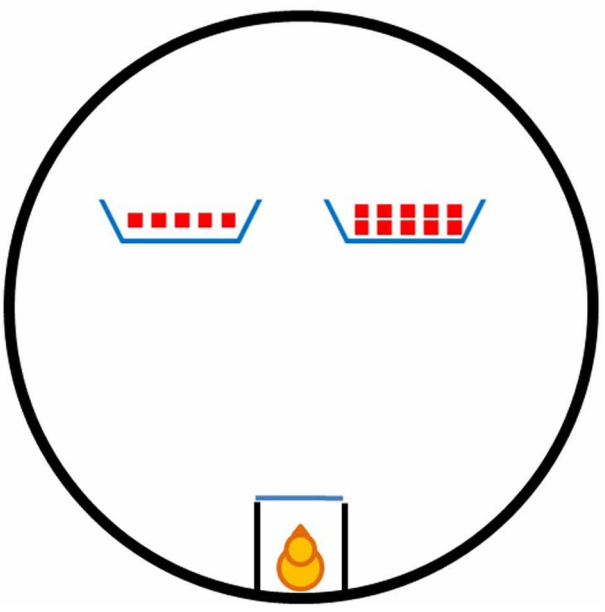


FIGURE 1 | The apparatus employed in both experiments. The holding box and the two screens are here represented in the arena just as they were during the testing session.

each trial. The box was made of opaque plastic sheets, with an open top allowing the insertion of the chick before each trial. The side of the holding box facing the center of the arena consisted of a removable transparent glass partition (20 × 10 cm), this allows the subjects, while confined, to see the inner of the arena. During the training phase a single opaque cardboard screen (16 × 8 cm; with 3 cm sides bent back to prevent the chicks from seeing objects hidden behind the screen) was used, positioned in the center of the arena, in front of and 35 cm away from the front of the holding box. During testing, two opaque cardboard screens (16 × 8 cm), identical in color and pattern (i.e., blue colored with an orange "X" on them), were positioned in the center of the arena, symmetrically with respect to the front of the confining box (i.e., 35 cm away from it, and 20 cm spaced apart from one another).

Procedure

Training. On day three of life, at around 12.30, chicks underwent a preliminary training session. Each chick, together with a single object, identical in color and dimension to the squares composing its imprinting stimulus, was placed within the testing arena, sitting in front of the starting box and facing the screen. The object was held from above by the experimenter (not visible to the chick), via a fine thread, and kept suspended 3–4 cm over the floor, at an intermediate position between the holding box and the screen (about 15 cm away from the screen). This initial phase lasted for 5 min, over this period the chick was free to move around and get acquainted with the environment. Thereafter, the experimenter slowly moved the object toward the screen, and then behind it, until it disappeared from the chick's sight. This procedure was repeated a few times, until the chick started to follow the object behind the screen as soon as it was made to disappear. Thereafter, the chick was confined within the holding box, from where it could see the object being moved behind the screen. As soon as the object had completely disappeared from sight, the chick was set free in the apparatus by lifting the transparent frontal partition. Every time the chick rejoined the object, as a reward, it was allowed to spend a few seconds with it. The whole procedure was restarted and the training ended when the chick had rejoined the object three consecutive times. On average, about 15 min were required to complete the training for each chick.

Testing. Testing took part 2 h after the end of training and it was composed of 20 trials. At the beginning of each trial, the chick was confined to the holding box with the transparent partition in place, from where it could see the two screens in the arena. The chick was presented with only one element at a time and could not see either set as a whole. Every element of the first set was placed about 10 cm from the front of the holding box and then it was made to disappear behind one of the screens. Immediately after it disappeared the next element was introduced into the arena. In this way, all the elements of the first set were made to disappear one by one behind the same screen. Then, the identical procedure was repeated for the second set behind the other screen. Each element was kept in front of the starting box for 3 s and then it took 3 s to be moved back behind the screen (6 s overall). About 2 s elapsed from the disappearance of one object and the appearance of the next one. 3 s after the disappearance of both sets, the transparent partition was removed and the chick was left free to move within the arena. In this way the whole procedure of stimuli presentation lasted about 121 s for each trial. The order the two sets were presented (which one was presented first) as well as the position where they disappeared (left or right screen) was counterbalanced within each chick's testing trials. At the end of stimuli presentation the chick was released in the arena by removing the frontal transparent partition and was allowed to look behind either of the two screens. A choice for one of the screens was defined as when the chick's head had entered the area behind the screen. Only the choice for the first screen visited was scored and thereafter the trial was considered over. At the end of each trial, as reward, the chicks were allowed to spend a few seconds with their "social companions" behind the screen chosen. The behavior of the chicks was entirely video-recorded and it was scored blind both online and later offline.

If the chick did not approach either screen within 3 min, the trial was considered null and void and it was repeated immediately afterwards. Whenever the chick failed to respond also at the second attempt of performing the trial, that trial was considered as null and recorded as such, this means that chicks could score less than 20 valid trials. In the first experiment two chicks scored 19 valid trials and two other chicks scored 18 valid trials, the remaining 14 subjects scored all 20 valid trials.

DATA ANALYSIS AND RESULTS

Previous literature showed that in this sort of task chicks have a clear tendency to approach the screen hiding the larger group of social companions (Rugani et al., 2009, 2011a,b, 2013a; Fontanari et al., 2011). Thus, we will henceforth define as "correct" the choice for the screen hiding the higher number of imprinting objects. We will similarly define the more numerous group of social companions as "target group."

This tendency to approach the larger group is also true for what concerns the performance of the group of chicks re-coded here (Rugani et al., 2011a). When the performance "no-control group" was compared with the chance level, it resulted that subjects preferentially chose the screen hiding 10 objects over the screen hiding 5 objects [$n = 10$; Mean = 69.423, s.e.m. = 2.693; one-sample t-test: $t_{(9)} = 7.213$; $p < 0.001$], or in the comparison 6 vs. 9, the screen hiding 9 objects over the screen hiding 6 objects [$N = 10$; Mean = 66.777, s.e.m. = 2.693; $t_{(9)} = 7.619$; $p < 0.001$]. Nevertheless the capability to solve proto-arithmetic calculations seems to be possible solely when numerical and quantitative cues were contemporary available. When the perimeter or the area were controlled for ("control group") we did not find any significant preference [5 vs. 10: $N = 8$; Mean = 53.263, s.e.m. = 2.320; $t_{(7)} = 1.407$; $p = 0.202$; 6 vs. 9: $n = 8$; Mean = 50.361, s.e.m. = 3.747; $t_{(7)} = 0.096$; $p = 0.962$].

A laterality index was calculated to represent the percentage of right-sided correct choices on the overall number of correct choices, according to the formula:

(Number of correct choices when the target group was on the right screen/Total number of correct choices) × 100.

The laterality index can assume values ranging from 0 (all correct choices performed when the target group is behind the left screen) to 100 (all correct choices performed with the target group

behind the right screen); a value of 50 indicates an equal number of correct choices on both sides (chance level).

The laterality index was analyzed by a 2 × 2 ANOVA with (between-subjects factors) Numerical Comparison ("5 vs. 10" and "6 vs. 9") and Control for Continuous Variables ("control" and "no control"). As since no significant effect for the factor Numerical Comparison [$F_{(1,\ 32)} = 1.910$; $p = 0.177$] nor an interaction between this factor and the Control for Continuous Variables [$F_{(1,\ 32)} = 0.017$; $p = 0.897$] was detected, data were collapsed in all further analyses and comparisons between groups were performed by an independent sample t-test for unequal variances (Ruxton, 2006). Laterality effects were assessed comparing the laterality index to chance level via one-sample t-tests.

Overall, chicks were significantly lateralized and performed a higher percentage of correct choices when the target was on the right position [$t_{(35)} = 3.777$, $p = 0.001$, mean = 63%, s.e.m. = 3%]. Such bias appeared to be more pronounced for chicks of the "control" rather than of the "no control" group (see **Figure 2**). However, only a marginally non-significant difference was detected between these two groups [$t_{19.99} = 1.949$, $p = 0.065$; mean of the "no control" group = 70%, s.e.m. = 6%; mean of the "control" group = 57%, s.e.m. = 3%, Cohen's $d = 0.642$]. Marginally non-significant results should of course be treated with caution given their difficult interpretation. Nevertheless, in the light of the pronounced difference between the mean score observed in the two groups, we run a separate analysis comparing the "no control" group with chance level. This allowed us to verify that a significant lateralization effect could be detected even in the group for which continuous variables were not controlled [$t_{19} = 2.53$, $p = 0.02$].

EXPERIMENT 2

In Experiment 1 we provide a first evidence in a non-human species of an advantage when the larger set is found to the right side of the subject. This bias could be due to an effect specific of numerical processing, or rather to a non-numerical preference when searching for social attractors on the right side. To control for this alternative explanation, in the present experiment, we analyzed the behavior of chicks tested according to the same paradigm, but with equal numbers of objects disappearing behind each screen. If the bias highlighted in Experiment 1 has a non-numerical basis, we would expect it to appear also here, when choice is not based on numerical cues as identical numbers of items are presented to the left and to the right side.

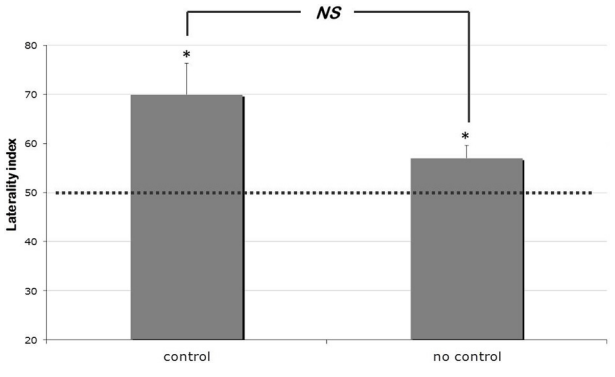


FIGURE 2 | Results of Experiment 1. Percentages of laterality index (means ± s.e.m.) scored by control and no-control group of chicks. The dotted line ($y = 50$) represents chance level. * indicates $p < 0.05$.

Both sets used in Experiment 2 were composed of two objects (i.e., the comparison was of 2 vs. 2). The numerosity of each set, hence the overall number of objects present, was smaller than in Experiment 1. Rearing conditions, however, were very similar in that chicks in both experiments were exposed to multiple (i.e., five or six) objects.

MATERIALS AND METHODS

Subjects and rearing conditions

For the present experiment we analyzed the behavior of a sample of 12 female domestic chicks (*Gallus gallus*). Behavioral data were originally collected by Fontanari et al. (2011). The experiment that we have re-coded here was originally designed to investigate if chicks were able to use property information (e.g., color) for object individuation, exploiting chicks' spontaneous tendency to approach the larger group of familiar objects. For this reason imprinting stimuli differed from Experiment 1, being composed of three green squares and three yellow squares (4 × 4 cm). Beside that, rearing conditions were identical to those previously described. This should not cause any difficulty for the comparison of the results of the present experiment and of Experiment 1, where objects of identical color were used. Indeed, for the chicks of Experiment 2 objects of both colors were familiar, in a comparable way with respect to Experiment 1, because both have been used during rearing and were treated as imprinting objects (Rugani et al., 2010a).

Training stimuli and procedure

Testing stimuli were green and yellow squares (4 × 4 cm). At each training trial only a single square (either a yellow one or a green one) was used. During training the two stimuli were used the same number of times. All the other training conditions were exactly the same described for the Experiment 1.

Testing stimuli and procedure

Test stimuli were identical to those employed during training. At each testing trial two pairs were sequentially presented (a low-variety and a high-variety pair). For the low-variety pair two identical squares (yellow + yellow or green + green) were used. For the high-variety pair two squares of a different color (yellow + green) were employed. The presentation of each pair proceeded as follows: the two objects were made to simultaneously appear from one screen, coming in front of the chick confined in the holding box and then made to slowly disappear behind the same screen. The whole procedure took approximately 20 s. After a delay of 5 s, the chick was set free within the arena. Ten test trials were administered to each chick.

The use in the two pairs of the color (yellow or green) of the objects was randomized between subjects, whereas the order of presentation of the two pairs as well as which screen concealed which pair were counterbalanced within subjects across subsequent trials.

No subjects performed null trial in this Experiment.

DATA ANALYSIS AND RESULTS

In this experiment chicks were not presented with a numerical discrimination, but rather with the choice between approaching either a screen hiding two identical social companions (low-variety pair), or a screen hiding two social companions differing in color from one-another (high-variety pair). We arbitrarily defined the high-variety pair as the target group. In order to compute a laterality index we thus applied the formula:

(Number of choices when the target group was on the right screen/Total number of choices for the target object) × 100.

A one-sample *t*-test was used to compare the laterality index with chance-level (i.e., with the value of 50%, indicating absence of lateralization). Contrary to what observed in Experiment 1, in the present experiment we were unable to detect any significant departure from chance level [$t_{(11)} = 0.379$, $p = 0.712$, mean = 52%, s.e.m. = 6%].

It should be noted that the absence of a significant effect in this case could be related to the minor number of subjects tested in Experiment 2. To assess this objection we have run two different analyses. First of all we computed the minimum number of subjects that would be required to reach a statistically significant effect, given the effect size observed in Experiment 1. A power analysis (G*Power 3.1 software) revealed that, assuming the standard power value of 0.8, at least 14 subjects would be required in a one-tailed *t*-test. That is, two subjects more than those employed in Experiment 2. The sample size of Experiment 2 is not far way from the desired N, nevertheless on the basis of this result we have to recognize that is not possible to rule out lack of statistical power as an explanation. Also, the results of the power analysis are crucially dependent on the arbitrary value assigned to the "power" parameter, and more conservative values would increase the dimension of the required sample size. However, these computations are of course based on the assumption that the same effects size computed for Experiment 1 applies also to Experiment 2. Another interesting approach is to compute the minimum sample size needed to reach significant departure from chance level, based on the values of Mean and SD actually observed in Experiment 2. This revealed that the number of subjects that would be required to reach a statistically significant effect in this Experiment would be of 620, greatly exceeding the sample size of Experiment 1. This speaks against the possibility to obtain drastically different results by increasing sample size of two units.

To conclude even if this second Experiment is not characterized by a strong power, nonetheless it seems to suggest that a number-space association could be there in this kind of task. On the grounds that non-significant results must be interpreted with caution, it is not possible to unequivocally conclude that our results reflect a precursor of the left-to-right mental number line orientation, but this investigation will be one of the most relevant scientific challenges in this field of research.

GENERAL DISCUSSION

Experiment 1 allowed us to detect a rightward bias, evident when domestic chicks are required to search for the larger number of objects in the comparisons 5 vs. 10 and 6 vs. 9. In contrast, Experiment 2 revealed that, when no numerical discrimination is involved in the task, chicks tested in the same apparatus and with a similar procedure to that described for Experiment 1, do not reveal any directional bias. This difference could be due to a number of reasons. First of all, set numerosities involved in Experiment 1, 2 were rather different, with large numerosities being employed in the first and small numerosities being employed in the second experiment. However we have no reasons to believe that small or large numbers of social companions trigger for qualitatively different processing. Moreover similar rearing conditions were used in the two experiments, exposing chicks in both cases to multiple objects. This procedure would activate the same cognitive system for the processing of both small and large numbers (Rugani et al., 2013a,b,c). A second issue concerns whether a preferential choice is or is not expressed by subjects for one of the two sets. Fontanari et al. (2011) (where from data of Experiment 2 come) reported lack of preference between two identical vs. two different objects. Absence of any significant lateralization in Experiment 2 may therefore depend on the lack of preference for one of the two sets. This hypothesis though would not be consistent with evidence provided in Experiment 1 of the present paper. In fact, chicks in the study of Rugani et al. (2011a) (where from data of Experiment 1 come) did not discriminate sets of 6 vs. 9 and 5 vs. 10 objects when continuous variables were controlled for. Nevertheless, in Experiment 1 a clear lateralization emerged for chicks tested in such condition. Indeed, chicks of the "control" condition tended to display an even more pronounced rightward bias than chicks in the "no control" condition. Both in Experiment 2 and in the "control" condition of Experiment 1 chicks did not show a significant preference for one of the two sets. Nevertheless, only when the two sets differed in numerosity, such as in Experiment 1, chicks emitted a higher number of correct choices if the larger set was on their right side.

It seems that a bias can be observed only when chicks have to choose between sets differing in numerosity. This evidence would support previous findings that animals map numerical values onto space, though it would demand an explanation beyond the hypothesis of attentional facilitation for the left hemispace. Further research is warranted for understanding this phenomenon, the effect should be replicated with other numerosities and with new control conditions, but most interestingly, new experiments should probe, within a same paradigm, both an advantage to respond to large numbers located to the right side as well as to small numbers located to the left side.

Here we have shown that chicks, in the attempt to rejoin the set with the higher number of social companions, performed better when this was located to their right side. This bias is reminiscent of the well-known phenomenon of the left-to-right orientation of number line in our species. Originally this orientation was thought to be dependent on cultural factors, such as the reading direction, making it implausible to observe a similar phenomenon in non-human animals (Dehaene et al., 1993). This interpretation is also supported by the fact that the association of smaller numbers with left space and larger numbers with right space is stronger in bilingual subjects after reading a Russian text (that is read from left to right) than after reading an Hebrew text (that is read from right to left; Shaki and Fischer,

2008). More recent investigations, however, suggest that reading habits themselves are unlikely to be the only origin of this spatial-numerical arrangement (Fischer and Brugger, 2011). For example, it is possible to reverse the spatial association for numbers merely by instructing observers to think of numbers as either indicating lengths on a ruler or time on a clock face (which have opposite horizontal mappings for small and large digits; Bächtold et al., 1998; Vuilleumier et al., 2004). Moreover, developmental studies suggests that preschool children already explore objects more efficiently when they are numbered in ascending order from left to right (Opfer and Furlong, 2011). Using a manual bisection paradigm, with lines flanked by arrays of dots, 5-year-old children showed the same bias of 7-year-old children and adults, indicating that the left-to-right mapping of numbers into space could emerge spontaneously and independently of formal instruction (de Hevia and Spelke, 2009).

Evidence suggestive of a left-to-right numerical orientation has been recently obtained also in non-human species. Domestic chicks and Clark's nutcrackers, trained to select a target element in a sagitally-oriented series and tested with a rotated series, identified as correct solely the element from the left end of the series (Rugani et al., 2007, 2010b, 2011b). This phenomenon, however, could be linked to a general bias for allocating attention in the left emispace, rather than to a specific lateralization of numerical representation (Rugani et al., 2011b). Here, employing a completely different paradigm, we reported a rightward bias that emerges when domestic chicks are required to search for the larger number of objects, in the comparisons 5 vs. 10 and 6 vs. 9 (Experiment 1). Such a bias was not found when the numerousness of the two sets were equated, in the comparison 2 vs. 2 (Experiment 2). Obviously, such an advantage for the right-hemispace cannot be explained as a byproduct of a leftward attentional prioritization. Although further evidence is necessary, we believe that the results presented in this paper provide the first evidence suggesting an orientation effect of purely numerical origin.

Interestingly enough, it is well known that in this species the level of lateralization is determined by the exposure of embryos to light during a critical period (from day 17 to 21 of incubation). Chicks hatched from light incubated eggs are strongly lateralized, whereas the lateralization is largely prevented in dark-incubated chicks (Daisley et al., 2009; Chiandetti, 2011). All chicks used in these Experiments came from a commercial hatchery, where eggs were maintained in darkness. However, sometimes the light was turned on in order to guarantee the routine maintenances, reducing the control over the degree of lateralization caused to the embryos. We thus consider these subjects as poorly lateralized, but, due to the not perfectly controlled incubation conditions, we are currently unable to draw strong conclusions about the role of light-exposure in this lateralization effect. This issue could be better investigated in future experiments with chicks obtained from light vs. dark laboratory-incubated eggs.

Overall these data suggest that a disposition to map the numerical magnitude from left to right may originate from a prelinguistic precursor. The phenomena associated with basic numerical competence seem to be rooted in biological primitives that can be explored also in very young animals. Some sort of a Kantian "a priori" intuition that precedes and structures how animals (human and non-human) experience the environment.

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Poor receptive joint attention skills are associated with atypical gray matter asymmetry in the posterior superior temporal gyrus of chimpanzees (*Pan troglodytes*)

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Clinical and experimental data have implicated the posterior superior temporal gyrus as an important cortical region in the processing of socially relevant stimuli such as gaze following, eye direction, and head orientation. Gaze following and responding to different socio-communicative signals is an important and highly adaptive skill in primates, including humans. Here, we examined whether individual differences in responding to socio-communicative cues was associated with variation in either gray matter (GM) volume and asymmetry in a sample of chimpanzees. Magnetic resonance image scans and behavioral data on receptive joint attention (RJA) was obtained from a sample of 191 chimpanzees. We found that chimpanzees that performed poorly on the RJA task had less GM in the right compared to left hemisphere in the posterior but not anterior superior temporal gyrus. We further found that middle-aged and elderly chimpanzee performed more poorly on the RJA task and had significantly less GM than young-adult and sub-adult chimpanzees. The results are consistent with previous studies implicating the posterior temporal gyrus in the processing of socially relevant information.

Keywords: joint attention, chimpanzees, superior temporal gyrus, brain asymmetry in cognition, brain development

At approximately 6–8 months of age, typically developing children begin to respond to a number of non-verbal socio-communicative cues, including gaze, pointing and verbal bids (Adamson, 1996; Flom et al., 2006; Leavens, 2012). These are sometimes referred to as receptive joint attention (RJA) skills. Individual differences in RJA skill have been linked to the subsequent development of early linguistic skills, including comprehension and production of language, as well as other cognitive abilities, such as imitation learning and theory of mind (Mount et al., 1989; Charman et al., 2000; Slaughter and McConnell, 2003). For example, a number of studies have shown that the age of onset of both the initiation of, and response to, joint attention cues predicts the rate of language development in typically developing children (Bates et al., 1975, 1987; Carpenter et al., 1998; Morales et al., 2000; Nichols et al., 2005; Whalen et al., 2006; Mundy et al., 2007; Brooks and Meltzoff, 2008).

Not only is RJA a universal trait in typically developing children, there is also evidence for its existence in great apes and other primates, suggesting it has a long evolutionary history. Studies in a number of laboratories have shown that Old and New World monkeys and apes will not only follow gaze (Brauer et al., 2005; Rosati and Hare, 2009), but can follow gaze around barriers, and follow manual pointing gestures to specific locations (Tomasello et al., 1999; Brauer et al., 2005; Amici et al., 2009). As with human infants (Moll and Tomasello, 2004), there are considerable individual differences in gaze following and RJA performance in nonhuman primates. For instance, Russell et al. (2011) examined, among a number of measures, gaze following on three trials in a sample of 83 chimpanzees. Fifteen percent of chimpanzees failed to follow gaze on all three trials, whereas 41% successfully followed gaze on all three trials. Herrmann et al. (2007, 2010) have reported similar individual differences in gaze following and comprehension of pointing responses in chimpanzees and bonobos.

Though the cognitive abilities of primates to respond to different socio-communicative cues are well documented, our understanding of the neural mechanisms underlying their expression are poorly understood. In the current study, we examined whether individual differences in RJA performance are linked to variation in the volume or asymmetry of the posterior superior temporal gyrus (p_STG) in chimpanzees. We focused on the p_STG as the cortical region of interest for several reasons. First, in Old World monkeys, single cell recording and reversible lesion studies have shown that neurons within the superior temporal gyrus and sulcus respond to certain social cues, such as eye gaze (Emery, 2000; Kamphius et al., 2009; Shepherd, 2010; Roy et al., 2012), and these results are consistent with

fMRI findings in humans (Williams et al., 2005; Itier and Batty, 2009). Second, atypical patterns of asymmetry in the p_STG have been described in clinical populations in which deficits in social cognition and perception are prominent endophenotypes, notably schizophrenia (Barta et al., 1997; Klar, 1999; Kwon et al., 1999; Hirayasu et al., 2000; Sommer et al., 2001; Dollfus et al., 2005) and autism spectrum disorder (ASD; Zilbovicius et al., 2006; Jou et al., 2010; Chen et al., 2011). Third, in a recent review, Mundy and Newell (2007) proposed that responding to joint attention is associated with regions in the posterior superior temporal lobe and portions of the parietal lobe. For instance, in human adults, Williams et al. (2005) performed fMRI on subjects when they were engaged in joint attention compared to non-joint attention processing and found a significant number of brain regions active, including the ventromedial left prefrontal cortex (BA44, BA45), superior temporal gyrus (BA22), superior frontal cortex (BA10) anterior cingulate cortex (BA24), and regions within the basal ganglia (putamen and caudate). In terms of preverbal infants, far less is known, but studies employing scalp recording methods, such as EEG and ERPs, have reported significantly greater activity in posterior temporal and parietal regions when responding to joint attention cues (Mundy et al., 2000). These collective findings led us to focus on the p_STG as a targeted region potentially associated with RJA performance.

Chimpanzees are particularly valuable model species for understanding the neurobiology of social cognition for several reasons. First, as noted above, they have well developed RJA skills and, like humans, their responses to different socio-communicative cues fall along a continuum. This study was designed to delineate several points on this continuum that might be useful for understanding human social cognition as it relates to different clinical population such as schizophrenia and ASD. Second, anatomically and cytoarchitectonically, there is considerable homology between the human and chimpanzee brain (Hopkins and Nir, 2010; Spocter et al., 2010; Hopkins, 2013). For instance, the sulcal landmarks used to quantify the planum temporale and planum parietale in humans and chimpanzees are nearly identical (Hopkins and Nir, 2010; Gilissen and Hopkins, 2013) and, like humans, chimpanzees show leftward asymmetries in these regions, which are not found in other nonhuman primate species (Gannon et al., 2008; Lyn et al., 2011).

To test the hypothesis of the role of p_STG in RJA proposed by Mundy and Newell (2007), we measured RJA skills in chimpanzees on a task developed by Dawson et al. (2002), previously employed with typically developing children, as well as those at risk for autism. We also quantified the gray matter (GM) volumes of the anterior and posterior, superior temporal gryus (STG) in these same chimpanzees. We hypothesized that if variation in RJA skills is associated with cortical organization within the STG, then significant differences would be found between chimpanzees that perform poorly compared to those who perform moderately or very well on this task. Based on previous results from structural and functional imaging studies, we further hypothesized that associations between GM volume and/or asymmetry would be specific to the posterior, but not anterior, region of the STG.

MATERIALS AND METHODS

SUBJECTS

Subjects for this study included 191 captive chimpanzees (*Pan troglodytes*) housed at either The University of Texas MD Anderson Cancer Center (UTMDACC) or the Yerkes National Primate Research Center (YNPRC) of Emory University. There were 114 females and 77 males housed in social groups that ranged in size from 2 to 13 individuals. The chimpanzees ranged in age from 8 to 53 years (Mean = 26.24, s.d. = 10.68). Based on the age range, we classified our chimpanzee sample into four age groups including sub-adult (8–16 years), young-adult (17–25), middle-aged (26–39 years) and elderly (40 years or older). Based on these cut points, there were 31 sub-adult, 75 young-adult, 55 middle-aged, and 30 elderly chimpanzees in the sample. The age groups cut-points were adopted from previous studies in captive chimpanzees (Herndon, 2009; Lacreuse et al., 2014). Subjects had access to both indoor and outdoor enclosures throughout the day and night, and participation in the study task was voluntary. All procedures were approved by the local Institutional Animal Care and Use Committees and followed the Institute of Medicine guidelines for use of chimpanzees in research.

PROCEDURE

Receptive joint attention

The task used to measure RJA was identical to one developed by Dawson et al. (2002) in human children. Experiments were conducted with subjects either independent of their social group or divided into subgroups of two or three individuals, where the non-focal animals did not distract or interfere with the testing of the focal subject. Each subject received four test trials and a diagram of the trial procedure is shown in **Figure 1**. The goal of the task was to assess the number of social cues needed to elicit an orienting response from the subject. To accomplish this, each trial consisted of three hierarchical steps with an increasing number of social cues provided to the subjects in order to elicit an orienting response.

At the onset of testing for each trial, the focal chimpanzee would sit calmly in front of the experimenter they would engage them in some type of husbandry behavior. This might include the chimpanzee showing their foot, hand, arm or some other body part for inspection. When the chimpanzee was compliant with these requests, it was given small pieces of food. When the experimenter sensed that the chimpanzee was socially engaged with them, they would stop interacting with them and look over their head for 5 s, then return to a neutral position and wait 5 s (Step 1). If the chimpanzee overtly oriented or looked back to where the experimenter had looked either during the cue or the 5-s following the trial was over and the subject was given a score of 1. If the chimpanzee failed to look during the 10-s response window in Step 1, the experimenter would re-engage the chimpanzee in the husbandry-type activities again until she again felt as though the subject was socially engaged. At this point, the experimenter would look over the subject's head again and this time point with an extended arm/finger toward an imaginary object behind them for 5 s (Step 2). After this, the experimenter returned to her sitting position and waited an additional 5 s for the chimpanzee to respond. If the chimpanzee oriented or looked

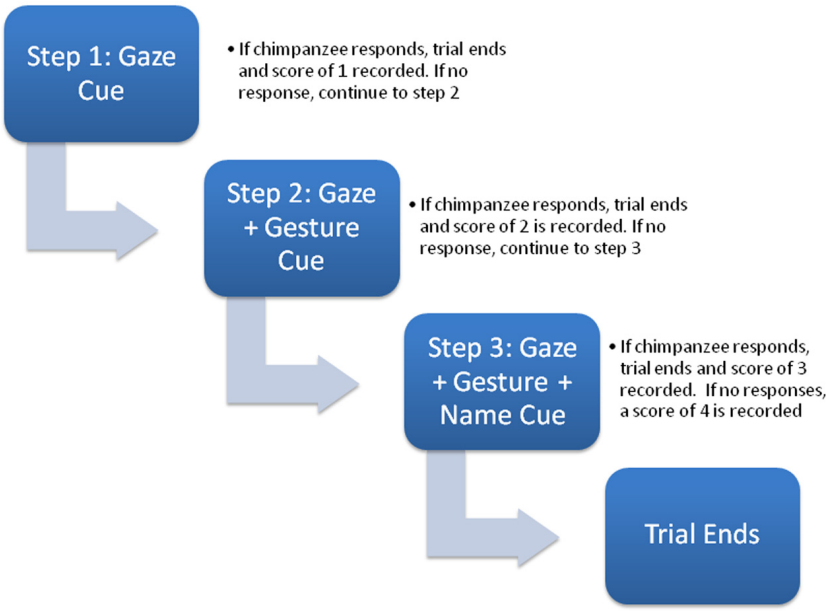


FIGURE 1 | Schematic diagram of the sequence of socio-communicative cues presented during each trial (see text for description).

back to where the experimenter had looked and pointed during the 10-s response window, the trial was over and the subject was given a score of 2. If the focal chimpanzee failed to look during the response window in Step 2, as before, the experimenter re-engaged the chimpanzee in the husbandry-type activities. The experimenter, then again, looked over the subject's head, pointed with an extended arm/finger toward an imaginary object behind them and said the chimpanzee's name two times (Step 3). The experimenter then returned to her neutral sitting position and waited 5 s for the chimpanzees to respond. If the chimpanzee oriented or looked back to where the experimenter had indicated during the 10-s response window, the trial was over and the subject was given a score of 3. If the chimpanzee failed to respond at the end of Step 3, it was given a score of 4. To characterize the performance of the chimpanzees, we derived a composite overall score that reflected the average number of cues they needed to respond. For this variable, the score of each trial was summed across trials and divided by the number of trials (4; Mean_RJA). Higher Mean_RJA indicated that subjects needed, on average, more social cues to elicit an orienting response across all trials.

MAGNETIC RESONANCE IMAGE COLLECTION

All chimpanzees were scanned during their annual physical examination. Magnetic resonance image (MRI) scans followed standard procedures at the YNPRC and UTMDACC and were designed to minimize stress. Thus, the animals were first sedated with ketamine (10 mg/kg) or telazol (3–5 mg/kg) and were subsequently anesthetized with propofol (40–60 mg/kg/h). They were then transported to the MRI scanning facility and placed in a supine position in the scanner with their head in a human-head coil. Upon completion of the MRI, chimpanzees were briefly singly housed for 2–24 h to permit close monitoring and safe recovery from the anesthesia prior to return to their home social group. All procedures were approved by the Institutional Animal Care and Use Committees at YNPRC and UTMDACC and also followed the guidelines of the Institute of Medicine on the use of chimpanzees in research. Fifty-seven chimpanzees were scanned using a 3.0 Tesla scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, PA, USA). T1-weighted images were collected using a three-dimensional gradient echo sequence (pulse repetition = 2300 ms, echo time = 4.4 ms, number of signals averaged = 3, matrix size = 320 × 320, with 0.6 × 0.6 × 0.6 resolution). The remaining 134 chimpanzees were scanned using a 1.5T G.E. echo-speed Horizon LX MR scanner (GE Medical Systems, Milwaukee, WI, USA). T1-weighted images were collected in the transverse plane using a gradient echo protocol (pulse repetition = 19.0 ms, echo time = 8.5 ms, number of signals averaged = 8, matrix size = 256 × 256, with 0.7 × 0.7 × 1.2 resolution).

REGION OF INTEREST

Prior to quantification of the anterior (a_STG) and posterior superior temporal gyrus (p_STG), all T1-weighted MRI scans were realigned in the AC–PC plane, skull-stripped and segmented into GM, white matter and Cerebral spinal fluid following procedures that have been described in detail elsewhere (Zhang et al., 2001; Smith et al., 2004). The superior temporal gyrus (STG) was primarily quantified in the coronal plane but, when necessary, the landmarks could be viewed simultaneously in the axial or sagittal plane using ANALYZE 11.0 software. The superior border of the STG was the sylvian fissure; the inferior border was the superior temporal sulcus and the lateral border was the surface of the temporal lobe (see **Figure 2**). Beginning at the temporal pole in each

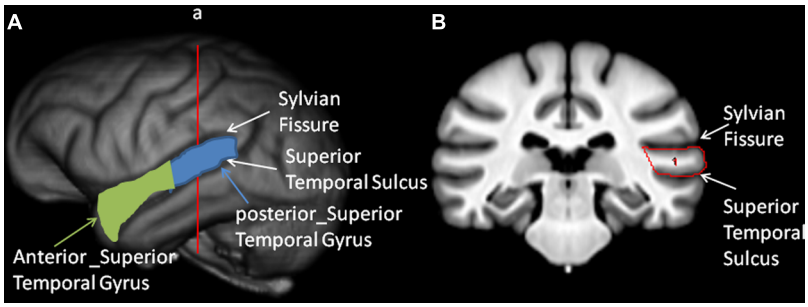


FIGURE 2 | Tracing of the anterior and posterior temporal lobe. Left panel: **(A)** 3-D reconstruction of the chimpanzee brain with the sylvian fissure (SF) and superior temporal sulcus (STS) labeled. Also, in green and light blue colors, the anterior and posterior superior temporal gyrus are outlined. Right panel: **(B)** Coronal view of the sulcl landmarks used to trace the superior temporal gyrus on a T-1 weighted MRI scan.

hemisphere, an object map was drawn around the gyrus using the landmarks described above. Moving posteriorly in 1 mm increments, the object maps were drawn on each image and continued until the sylvian fissure or superior temporal sulcus terminated. In some cases, the posterior sylvian fissure bifurcated into an ascending and descending branch, and we always followed the descending ramus as the superior border of the STG. To divide the STG into anterior and posterior regions, the total length of the gyrus, which corresponded to the number of images on which an object map was drawn, was determined and the median slice was identified. Images lower or equal to the median were defined as the a_STG region and images higher than the median were defined as the p_STG. The median slice was typically found at or about the anterior location of Heschl's gyrus (HG). The object maps for each subject and hemisphere were saved. To calculate the GM volume of the a_STG and p_STG, the object maps that were traced on the T1-weighted scan for each hemisphere and region were applied to the segmented GM volume (see **Figure 2B**). The left and right hemisphere volumes (mm^3) were computed by summing all the voxels found within the a_STG and p_STG object maps. All the images were traced by a single individual (MM) and prior to data collection, intrarater agreement was established using intraclass correlation coefficients within a sample of 10 individual brains. Intraclass correlations were positive and significant for both the left ($r = 0.922$, $p < 0.01$) and right ($r = 0.972$, $p < 0.05$) hemispheres. The person (MM) tracing the brains was blind to the sex and individual performance of the chimpanzees on the RJA task.

DATA ANALYSIS

For each subject, we computed a percentage of GM volume by dividing the a_STG and p_STG GM values by the total GM volumes within each hemisphere. This was done to adjust for potential individual differences in total GM independent of the regions of interest. The percentage scores were averaged between the two hemispheres to create an overall estimate of GM for each region. In addition, we also computed asymmetry quotients (AQ) for GM within each region (GM_AQ_Ant, GM_AQ_Post). AQ scores were computed following the formula: $[AQ = (R - L)/((R + L) \times 5)]$ where R and L represent the respective GM percentages for the right and left hemispheres. Positive AQ values reflect right hemisphere biases and negative values reflect leftward asymmetries. The absolute value of the AQ indicates the strength or magnitude of the asymmetry. All analyses were performed using inferential statistics with alpha set to $p < 0.05$. *Post hoc* analyses, when necessary, were conducted using Tukey's Honest Significant Difference test.

RESULTS

RECEPTIVE JOINT ATTENTION

In the initial analyses, we tested for sex and age effects on the Mean_RJA performance. For this analysis, we used analysis of variance with sex and age group as the between group factors, while the Mean_RJA scores were the dependent measure. We found a significant main effect for sex $F(1,183) = 4.288$, $p < 0.04$ and a significant interaction between sex and age group $F(3,183) = 4.364$, $p < 0.006$. The mean Mean_RJA performance for males and females from each age group are shown in **Table 1**. *Post hoc* analysis indicated that elderly females did significantly worse than middle-aged, young-adult and sub-adult females. For males, elderly and middle-aged individuals did significantly worse than young-adult and sub-adult apes.

STG VOLUME AND ASYMMETRY

We examined the effects of sex and age on STG volume and asymmetry. In the volumetric analysis, we used a mixed-model ANOVA with the standardized GM *z*-scores for the anterior and posterior STG serving as the repeated measure, while sex and age group were the between-group factors. This analysis revealed significant main effects for sex $F(1,183) = 6.661$, $p < 0.02$ and age $F(3,183) = 2.837$ $p < 0.04$. There was also a significant interaction between sex and temporal lobe region $F(1,183) = 5.316$, $p < 0.03$. For the age main effect, *post hoc* analysis indicated that elderly chimpanzees had smaller GM volumes compared to sub-adult and young adult, but not middle-aged chimpanzees. The mean percentage GM volumes in each group are shown in **Table 1**. For the interaction between sex and temporal lobe region, *post hoc* analysis indicated no significant difference in GM volume for the a_STG region; however, for the p_STG region, males (Mean = 2.27, SE = 0.054) had relatively less GM than females (Mean = 2.56, SE= 0.054). No other significant main effects or interactions were found.

Table 1 | Average Mean_RJA and percentage GM volumes (+SE) for male and female chimpanzees in each age group.

	Age groups			
	Sub-adult	**Young-adult**	**Middle-aged**	**Elderly**
Mean_RJA				
Females	1.95	1.99	1.81	2.63
	(0.19)	(0.14)	(0.14)	(0.18)
Males	2.21	2.13	2.85	2.33
	(0.23)	(0.14)	(0.20)	(0.28)
Overall	2.08	2.06	2.33	2.48
	(0.15)	(0.09)	(0.12)	(0.16)
Percentage GM volume				
Females	2.68	2.58	2.56	2.32
	(0.11)	(0.05)	(0.06)	(0.09)
Males	2.55	2.34	2.28	2.19
	(0.13)	(0.07)	(0.11)	(0.15)
Overall	2.62	2.46	2.42	2.26
	(0.08)	(0.05)	(0.07)	(0.09)

For asymmetries in the a_STG and p_STG, we also used a mixed model ANOVA with the AQ scores for each region serving as the repeated measure while sex and age group were the between group factors. A significant main effect for region was found $F(1,183) = 27.624$, $p < 0.001$. The mean AQ scores for the p_STG region (Mean $= -0.080$, SE $= 0.013$) were more leftward than the a_STG region (Mean $= 0.023$, SE $= 0.013$). Indeed, one sample t tests on the AQ scores revealed a significant population-level leftward bias for the p_STG $t(190) = -7.214$, $p < 0.001$, but no significant bias for the a_STG region $t(190) = 0.709$, $p = 0.479$.

RELATIONSHIP BETWEEN MEAN_RJA AND STG VOLUME AND ASYMMETRY

In the next set of analyses, we integrated the measures of GM volume and asymmetry for the a_STG and p_STG regions into a series of partial correlation analyses as a means of predicting individual differences in RJA performance. Because we previously showed that age and sex influenced RJA performance, we sought to determine whether variation in either GM volume or asymmetry would account for a significant proportion of variability in performance over and above that of the variables of sex and age. Thus, we performed partial correlation coefficients between Mean_RJA performance and the a_STG and p_STG standardized GM volumes and AQ scores. The only significant partial r-value was between Mean_RJA performance and p_STG AQ scores ($beta = 0.155$, $p < 0.04$). Subjects with more rightward AQ scores showed poorer RJA performance.

RELATIONSHIP BETWEEN GAZE PERFORMANCE ALONE AND STG VOLUME AND ASYMMETRY

The previous analyses focused on the association between Mean_RJA performance and variation in GM volume and asymmetry in the a_STG and p_STG regions. Because gaze following and response to gaze cues alone are important factors linked to variation in p_STG organization, we further examined whether performance on the gaze-following cue alone was associated with the neuroanatomical measures. For this analysis, we computed the number of trials on which the chimpanzees responded to the gaze cue alone. Scores could range from 0 to 4 (a 4 was recorded when the subject responded to gaze alone on all four trials). Based on these data, and in order to increase statistical power, we classified the chimpanzees into one of three groups, including poorer than average (score = 0, PTA_Gaze), average (score = 1 or 2, AVG_Gaze) or better than average (score of a 3 or 4, BTA_Gaze). We then compared the a_STG and p_STG volume and asymmetry scores between these groups as well as between sexes and age groups using analysis of variance. No significant main effects or interactions were found between gaze performance, sex and the a_STG and p_STG GM volume measures; however, for the AQ scores, we found a significant main effect for gaze performance on the p_STG scores $F(2,167) = 4.054$, $p < 0.02$. The mean p_STG AQ scores for the BTA_Gaze, AVG_Gaze, PTA_Gaze groups are shown in **Figure 3**. *Post hoc* analysis indicated that the mean p_STG AQ scores were significantly more leftward for the BTA_Gaze group compared to the PTA_Gaze group but did not differ from the AVG_Gaze group. No other significant differences were found. For the a_STG AQ scores, no significant main effects or interactions were found.

DISCUSSION

The results of this study reveal several important findings. First, poorer performance on a task designed to assess RJA is associated with greater rightward asymmetries in the posterior, but not anterior, portion of the superior temporal gyrus. Second, we found significant age-related changes in performance on the RJA task and overall GM volume within the superior temporal gyrus. For the RJA task, older subjects performed more poorly than younger subjects. Further, the onset in decline on performance started at a younger age in males compared to females. For the GM volume, older subjects had lower percentages of GM compared to younger individuals.

With regard to the association between RJA and gaze performance and atypical asymmetries in the p_STG, our findings in chimpanzees are consistent with the hypothesis proposed by Mundy and Newell (2007), and are in general agreement with results in human clinical populations in which deficits in socio-communicative abilities are a significant endophenotype, such as schizophrenia (Sommer et al., 2001) or ASD (Boddaert et al., 2004; Zilbovicius et al., 2006). To be clear, we are not suggesting that our chimpanzees that respond poorly to socio-communicative cues are schizophrenic or autistic but rather that individual variation in RJA performance appears to be explicitly linked to asymmetries in the p_STG, but not the a_STG. We emphasize the word atypical asymmetry in this discussion because it is important to emphasize that the chimpanzees, as a group, show a leftward asymmetry in the GM volume of p_STG. Thus, individuals who fail to show a bias, or those with reversed asymmetries in the p_STg, are the ones who perform poorly on the RJA task.

The finding of a significant association between RJA task performance and atypical asymmetries in the p_STG also bears

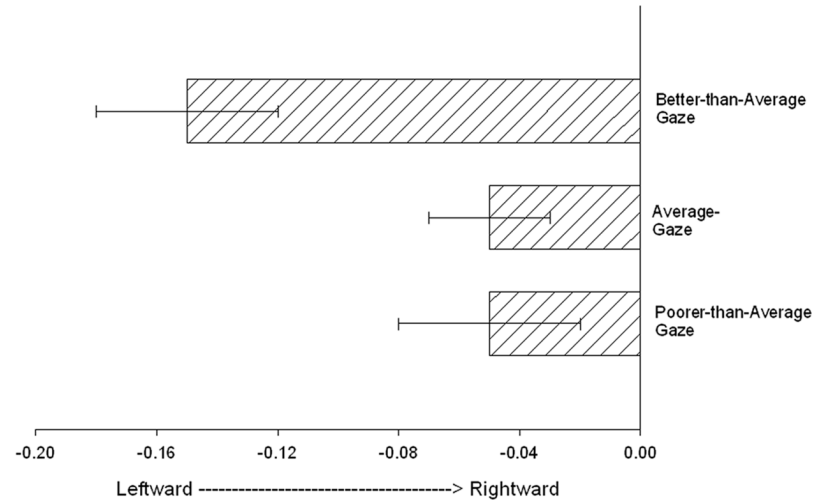


FIGURE 3 | The mean posterior superior temporal gyrus (p_STG) AQ scores (+/− standard error) for the Better-than-average_Gaze, Average_Gaze, Poorer-than-average_Gaze groups.

directly on theoretical and applied views of the role of brain asymmetries on individual fitness. A number of researchers have argued that having an asymmetrical brain confers some advantages from an evolutionary perspective (Ghirlanda and Vallortigara, 2004; Vallortigara and Rogers, 2005). With the context of the results reported here, it might be suggested that having an asymmetrical p_STG (and indeed, a leftward asymmetry) provides individuals with increased sensitivity for monitoring socio-communicative cues from conspecifics, such as gaze direction, head orientation and gestures. Many of these cues would be potentially important for selecting mates and/or avoiding conflict and agonistic encounters with conspecifics, and therefore afford some advantages to those individuals.

We also found age-related changes in both RJA performance and standardized GM volume. With respect to RJA, older chimpanzees performed more poorly than younger individuals. Similarly, older individuals had lower standardized GM volumes than younger individuals (see **Figure 2**). There is very little data on age-related changes in cognition and cortical organization in chimpanzees, but the findings reported here are partially consistent with existing data, though they also differ in some important ways. Recently, in a sample of 36 female chimpanzees, Lacreuse et al. (2014) reported age-related changes in response to gaze following, with older subjects performing more poorly. The results reported here are largely consistent with this finding, though in a much larger sample of chimpanzees that also included males. The inclusion of males was relevant in the present study because the findings showed that the decline in RJA performance occurred at an earlier age in males than it did in females. Life history and survival tables for chimpanzees have shown pronounced sex differences in life span, with males dying, on average, 7 years earlier than females (Dyke et al., 1995; Hill et al., 2001). Thus, the early decline in RJA performance abilities in males compared to females is consistent with the differences in relative life span and mortality between the sexes.

The evidence for age-related decline in the GM volume within the temporal lobe is, as far as we know, the first compelling evidence of age-related decline in cortical organization in chimpanzees. Several studies in chimpanzees that have examined age-related decline in total brain volume and weight, white matter volume, frontal lobe gray and white matter volume and hippocampal volume have failed to find age-related changes (Herndon et al., 1999; Sherwood et al., 2011; Chen et al., 2013). Therefore, the significant effect of age on GM volume was not anticipated and certainly contradicts previous findings in chimpanzees. However, the data presented here differ from these previous studies in two important ways that might explain the discrepancy in findings. First, we had a much larger sample size than previous studies (previous largest sample size was $n = 97$), particularly among males and individuals within the elderly group. Second, we focused on the temporal lobe GM in this study, a region that has not, until now, been explicitly quantified in previous studies examining age-related changes in cortical organization in chimpanzees.

In summary, individual differences in RJA performance was associated with in GM asymmetries in the p_STG in chimpanzees. These findings are consistent with evidence of the role of the posterior superior temporal lobe in the processing of socially relevant information in humans and monkeys. What factors or mechanisms underlie both variation in RJA performance and p_STG asymmetries are not clear from this study, but the findings indicate that additional consideration and investigation are warranted. We would further add that this study focused only on anatomy, but examining the functional role of the p_STG in relation to RJA performance should be explored in future studies as a means of understanding the ontogenetic and phylogenetic factors that underlie the perception of socially relevant communicative cues in primates, including humans.

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An overview of human handedness in twins

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There has been a long-standing debate on the complex correlation between the development of human hand preference and brain lateralization. Handedness, used as a proxy for cerebral lateralization, is a topic of considerable importance because of its potential to reveal the mechanisms of the underlying pathophysiology of problems related to brain development or cognitive systems. Twin studies, which represent an important method of research in human genetics, would provide valuable suggestions to the studies on the relationship between lateralization and cognitive systems. Many studies have been performed using twin subjects; however, the results are inconsistent, partly because of sample size, background assumptions, data limits or inaccuracies, incorrect zygosity classification, and/or lack of birth histories. In summary, within the long history and large number of twin studies performed on handedness, a surprisingly large number of controversial findings have been reported, suggesting the complicated nature of this phenotype. In this mini review, the wide variety of twin studies on human handedness performed to date are introduced.

Keywords: twin study, laterality, handedness, brain asymmetry, zygosity, monozygotic twins, brain lateralization, human behavior

INTRODUCTION

Approximately 90% of humans are right-handed, with the rest made up of left-handed and ambidextrous individuals. It is well established as to singletons that the prevalence of left-handedness in males is slightly higher than that in females (Papadatou-Pastou et al., 2008). There has been a long-standing debate on the complex correlation between the development of human hand preference and brain lateralization. Handedness, used as a proxy for cerebral lateralization, is a topic of considerable importance because of its potential to reveal the mechanisms of the underlying pathophysiology of problems related to brain development or cognitive systems. Twin studies, which represent an important method of research in human genetics, would provide valuable suggestions to the studies on the relationship between lateralization and cognitive systems.

This Mini Review summarizes the twin studies of human handedness laterality, and touches on the relevant research factors such as twin type, chorion and placentation types, zygosity, gender effects, birth-order effects, handedness discordance, and brain measures using magnetic resonance imaging (MRI) and functional MRI (fMRI). Genetic twin analyses of the origins of handedness were not included. The relationship between handedness and disease is omitted here, as it is beyond the scope of this brief review. Other human laterality, such as footedness, is also excluded because of an insufficient number of twin studies to date.

TWINS AS SUBJECTS FOR THE STUDY OF HUMAN HANDEDNESS

There are two types of twins, and these types have completely different origins. Monozygotic (MZ) twins derive from the division of a single zygote, whereas dizygotic (DZ) twins derive from the independent release and subsequent fertilization of two ova (Machin, 1994). Handedness itself may be included as one of the anthropometric traits in similarity diagnosis (Segal, 1984).

It is commonly assumed that separation takes place in the early days of multicellular embryo development rather than at the initial zygote stage. If this split occurs within the first 72 h, the result is dichorionic monozygotic (DC-MZ) twin pregnancy. If the split takes place from 3 to 12 days after fertilization, a monochorionic monozygotic (MC-MZ) twin pregnancy is produced (Machin, 1994). Twin-twin transfusion syndrome (TTTS) is a serious condition that affects 10 to 15% of twin pregnancies with MC diamniotic placentation, resulting from the shunting of blood from one twin (the donor) to the other (the recipient) through placental vascular anastomoses.

MZ twin pairs share 100% of their DNA sequence, which means that most variation in pairs' traits is due to their unique or shared environment. DZ twin pairs share about 50% of their polymorphisms. DZ twin pairs are helpful to study because they tend to share many aspects of their environment by virtue of being born in the same time and place. Twin studies help disentangle the relative importance of environmental and genetic influences on individual traits and behaviors by comparing the similarity of MZ and DZ twin pairs, although they may differ due to fetal development and birth histories. For example, large birth weight differences in TTTS may indicate neurological risk in the smaller twin.

PREVALENCE BETWEEN TWINS AND SINGLETONS IN THE SAME POPULATION

Many studies (Tambs et al., 1987; Ellis et al., 1988; Williams et al., 1992; Coren, 1994; Davis and Annett, 1994) suggested that the prevalence of left-handedness is higher in twins compared

to singletons for several hypothesized reasons, i.e., intrauterine crowding, mirror-imaging, and pre- and/or perinatal damage.

According to Springer and Searleman (1980), in a compilation of 15 studies of handedness distribution, the mean proportions of left-handedness are as follows: singletons, 8.5%; DZ twins, 14.0%; and MZ twins, 14.5%. However, twins and singletons are seldom: assessed using the same handedness criteria, recruited in the same manner, or matched for age and sex (McManus, 1980).

Twins are more likely than singletons to be born prematurely and/or to experience perinatal injuries, and it has been suggested that the increase in left-handedness in neurologically intact twins reflects one end of the spectrum of the pathological left-handedness syndrome as formulated by Satz (1972). They suggested that twin populations may include two types of left-handers: natural and pathological (although firm evidence to support this view is lacking, but cf. Gurd et al., 2013).

SPECIFIC FACTORS FOR TWINS

CHORION TYPE OR PLACENTATION

Ever since Newman (1928) it has been speculated that delayed embryo splitting of MZ is associated with mirror-imaging effects if the division occurs after the establishment of an axis of bilateral symmetry. In such a situation, opposite handedness in the same pair of twins is expected, and discordant pairs in terms of handedness are expected to be more frequent in MC-MZ than DC-MZ pairs.

In a sample of 44 pairs of MZ twin children, consisting of 23 MC-MZ and 21 DC-MZ selected from hospital records, 18% of MC-MZ pairs were discordant pairs, and 26% of DC-MZ pairs were discordant (Sokol et al., 1995). Carlier et al. (1996), using 20 MC-MZ and 24 DC-MZ twin pairs, also reported a similar tendency in that the MC-MZs and DC-MZs differed neither in the frequency of discordant pairs nor in handedness, laterality measurements, or manual performance, suggesting that there was no chorion type effect. The largest study to date by Derom et al. (1996), using 254 MC-MZ pairs and 121 DC-MZ pairs, found no chorion effect on left-handedness. Several twin studies use another useful proxy variable of chorion type, namely placentation. Medland et al. (2003) and Ooki (2006) both found no effects of placentation on handedness using large populations of twin subjects. However, handedness was not actually experimentally tested in these studies, which used only verbal report.

Reviews of the literature examining handedness in twins by McManus (1980) and Sicotte et al. (1999) found no support for the theory of mirror-imaging. It is possible that the early support of this theory may be confounded by the inaccuracy of zygosity determination, since some investigators regarded discordant handedness as a marker of zygosity (Carlier et al., 1996; Sicotte et al., 1999). Some 20–25% of MZ twin pairs have discordant handedness (McManus, 1980; McManus and Bryden, 1992; Annett, 2002). Although numerous individual cases of mirror-imaging twins with discordant handedness have been reported (Sommer et al., 1999, 2002), discordant handedness in MZ twin pairs is not currently thought to represent a mirror-imaging phenomenon in general.

ZYGOSITY

If perinatal complication is related to left-handedness, the prevalence of left-handedness in MZ should be higher than that in DZ, because MZ, especially MC-MZ, biologically have more birth complications (Machin, 1994). With improvements in neonatal medicine, this may no longer be the case.

According to the review by McManus (1980) of 18 studies performed between 1924 and 1976, a total of 15% of 5,140 MZ and 13% of 4,436 DZ twins were left-handed. The only evidence in favor of MZ twins having a higher prevalence of left-handedness than DZ twins was obtained prior to 1930, when classification of laterality was not entirely independent of zygosity determination. It is clear that further study is warranted.

According to the meta-analysis of Sicotte et al. (1999), there exists no zygosity difference between MZ and DZ individuals, with a few individual outliers of the earlier studies. They concluded that there is nothing specific about the MZ twinning process *per se* that contributes to an excess of left-handedness in twins. Basso et al. (2000) found that there was a similar frequency of non-right-handedness in MZ (8.0%) and same-sex DZ (7.8%) twins born between 1900 and 1910. Orlebeke et al. (1996) observed a slightly higher prevalence of left-handedness in MZ male pairs (15%) compared to MZ female pairs (13%), DZ male pairs (13%), and DZ female pairs (13%). On the other hand, most recent studies with large populations (Medland et al., 2003; Ooki, 2006; Vuoksimaa et al., 2010) found no differences in handedness between MZ and DZ same-sex females nor between MZ and DZ same-sex males.

SEX OF CO-TWIN: TESTOSTERONE HYPOTHESIS

According to Vuoksimaa et al. (2010), there exist two opposite hypotheses regarding testosterone levels and handedness. According to the Geschwind–Behan–Galaburda hypothesis (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985), high levels of testosterone may inhibit the development of the left hemisphere and enhance the development of the right hemisphere. This can shift handedness and language functions from the left hemisphere to the right, resulting in weaker dextrality or left-handedness. Because testosterone is thought to pass between twins in utero, it was predicted that females with a male twin would show a high incidence of sinistrality compared to females with a female twin. Similarly, it was predicted that males with a male twin would be more likely to be sinistral than males with a female twin.

Götestam et al. (1992), in line with this hypothesis, reported that the prevalence of twins was lower among male homosexuals than in the general population, and explained that prenatal testosterone levels do not drop as dramatically in twins as they do in single fetuses, thereby counteracting the low levels of testosterone that could lead to homosexuality; a view not without controversy.

In contrast to the Geschwind–Behan–Galaburda hypothesis, an alternative theory suggests that left-handedness is caused by decreased levels of testosterone (Witelson and Nowakowski, 1991). This callosal theory proposes that low prenatal testosterone levels result in regressive development of the temporo-parietal regions of the brain, resulting in a larger isthmus of the corpus callosum and less functional asymmetry, thus increasing left-handedness. This

view requires several leaps of faith: that testosterone is causally related to temporo-parietal development; that this in turn is causally related to callosal size, and that size of the callosal isthmus is causally related to functional asymmetry in the directions prescribed (cf. Gurd and Cowell, 2013; Gurd et al., 2013 for alternate lines of evidence, albeit on a small scale).

Three studies (Elkadi et al., 1999; Ooki, 2006; Vuoksimaa et al., 2010) have directly compared the rate of left-handedness between females from opposite-sex and same-sex twin pairs. According to Elkadi et al. (1999) measures of the strength of hand preference and the incidence of sinistrality revealed no difference between opposite-sex and same-sex twins for either sex. According to Ooki (2006), no effect of the sex of the co-twin was observed in either males or females. Medland et al. (2009) found no difference in the prevalence of left-handedness between twins from same-sex and opposite-sex pairs in a series of increasingly constrained models testing for differences in prevalence.

Vuoksimaa et al. (2010) tested for differences in the rates of left-handedness or right-handedness in female twins from same-sex and opposite-sex twin pairs. They found a significantly lower prevalence of left-handedness in females from opposite-sex pairs (5.3%) compared to females from same-sex pairs (8.6%). Their results support the callosal hypothesis and are difficult to fully explain by postnatal factors, but they offer support to the theory that relates testosterone to the formation of handedness, and in a population-based sample, are suggestive of the effects of prenatal testosterone transfer.

BIRTH ORDER WITHIN TWINS: FIRST BORN vs. SECOND BORN

There are different risks to being first and to being second born within twin pairs – both carry risks. The first born has to prepare the birth canal, the second born, if larger and with a significant delay – may be at higher risk of anoxia – for vaginal deliveries. In a random sample of 104 pairs of handedness-discordant twins of 6 years of age or older, a significant relationship has been found between birth order and handedness in MZ twins, there being an excess of left-handed individuals among first-born twins. No such relation has been found in DZ twins (Christian et al., 1979). On the other hand, Boklage (1981) observed a 1.8-fold higher prevalence of left-handedness in the second-born members of same-sex discordant pairs, suggesting the secondary effect of hypoxia or acidosis. The effect of birth order within twin pairs has been intensively discussed (Orlebeke et al., 1996; James and Orlebeke, 2002). Most studies with large sample size (Derom et al., 1996; Elkadi et al., 1999; Medland et al., 2003; Ooki, 2006; Vuoksimaa et al., 2010) found no significant differences between first- and second-born twins in terms of left-handedness.

HANDEDNESS DISCORDANT MZ TWIN STUDY: CO-TWIN CONTROL STUDY

MZ twin pairs with discordant handedness are as genotypically alike as it is possible to be, and it is therefore possible to study the consequences of phenotypical left or mixed handedness with the ideal set of controls: namely, the right-handed twin members.

Clark et al. (1986) attempted to determine if the discrepancy in measured intelligence between MZ twin pairs concordant for handedness differed measurably from the discrepancy between MZ twin pairs discordant for handedness. Eight sets of MZ twins were examined, and no evidence was found to support the influence of pathogenic congenital factors on handedness. Segal (1989) compared three types of IQ scores for 67 young MZ twin pairs organized according to concordance or discordance for handedness and relative birth weight. The results support the hypothesis that left-handedness in lower-birth-weight MZ co-twins may be associated with pre-natal pathological events, while left-handedness in higher-birth-weight left-handed MZ co-twins may be associated with delayed zygotic splitting and disrupted asymmetry determination. Jäncke and Steinmetz (1995) examined 20 MZ twin pairs of whom 10 pairs were concordantly right-handed and 10 pairs discordant for handedness to determine whether the absolute degree of asymmetry of hand motor performance may have a heritable component. They found that at least in MZ twins the degree of hand motor asymmetry is mainly determined by non-genetic factors, whereas overall hand motor skill is more likely to be influenced by genetic factors. Kee et al. (1998) constituted a multitask appraisal of cerebral hemisphere specialization with 13 MZ twin pairs discordant for handedness, and found that asymmetries for left- and right-handed MZ twins were more similar to patterns reported in the literature for left- and right-handed singletons, respectively, than for opposite-handed co-twins. Gurd et al. (2006) examined 20 female MZ twin pairs discordant for handedness, and found that in the hand-preference inventories, the right-handers were more strongly lateralized that their left-handed sisters, and that the left-handers had greater variation in their laterality scores. They concluded that the analyses not only revealed obvious strong main effects of writing hand on performance tasks, but also interaction effects of handedness on the peg-moving task. Gurd et al. (2013) recently, using 26 handedness discordant MZ twin pairs, reported significant correlation between language-specific functional laterality in inferior and middle frontal gyri, and anterior corpus callosum. Häberling et al. (2012), using 35 MZ twin pairs of whom 17 pairs were concordant for handedness and 18 pairs discordant for handedness, suggested that handedness and hemispheric dominance for speech production might be at least partly dependent on genetically controlled processes of axonal pruning in the corpus callosum.

HANDEDNESS AND OTHER ASYMMETRY MEASURED BY MRI/fMRI

Several researchers used handedness as a marker of intrauterine neurological development and compared the handedness and brain asymmetry using fMRI. MZ twin pairs are often examined as an initial step toward documenting the nature of laterality. The report of Sommer et al. (1999) pointed out that in diseases in which cerebral lateralization is important to the pathology, the assumption that MZ twins share cerebral hemispherical functions is false due to the occurrence of mirror-imaging.

Sommer et al. (2002) studied language lateralization measured by fMRI in 12 MZ twin pairs who were concordant for handedness and 13 MZ twin pairs discordant for handedness, and claimed that high intra-pair correlation for language lateralization in the handedness-concordant twins suggests a genetic

basis for language lateralization, although they did not indicate the ages of the twins tested. However, in MZ twin pairs with discordant handedness, discordance for language lateralization occurs in a significant number of twins, consistent with a view that discordant language dominance may be caused by a relatively late splitting of the original embryo. Lux et al. (2008) examined the nature of hemispheric lateralization for neural processes underlying verbal fluency and visuo-spatial attention using a single pair of handedness discordant MZ twins. They found that the right-handed twin had left-lateralized verbal with right-lateralized visuo-spatial attention, while the left-handed twin had right-lateralized verbal with left-lateralized visuo-spatial activation. Rosch et al. (2010) examined cerebellar asymmetry in a pair of MZ handedness-discordant twins and found that the left-handed twin showed clockwise directional torque in the cerebral and cerebellar regions, while the right-handed twin showed disparate directions of cerebral (counter-clockwise) vs. cerebellar (clockwise) torque.

Geschwind et al. (2002) measured frontal, temporal, parietal, and occipital brain volumes and examined the relationship between cerebral asymmetry and handedness of 72 MZ and 67 DZ twin pairs. They found that genetic factors contributed twice the influence to left and light cerebral hemispheric volumes in the non-right-handed twin pairs.

CONCLUSION

It is often said that twin study represents a way of doing experimental research in a natural setting. Many studies have been performed using twin subjects; however, the results are inconsistent, partly because of the small sample size used or faulty assumptions in theoretical models (cf. McManus et al., 2013). Nevertheless, almost all studies that have examined the prevalence of twins in the general population have shown a higher frequency of left-handedness in twins than in singletons (Vuoksimaa et al., 2009). With recent advances in neuroimaging, such as MRI, fMRI, and DTI (diffusion tensor imaging), many co-twin control studies on the relationship between handedness and brain asymmetries have been intensively performed (Badzakova-Trajkov et al., 2010; Häberling et al., 2013; Gurd et al., 2013; Gurd and Cowell, 2013). But the sample size is still not very large and hence the statistical power is insufficient and some important information related to cerebral asymmetry or handedness is not always presented. Considering the small sample size, not only a heritability study, but also more detailed case reports, especially including the pre-/perinatal conditions of each twin, may be useful. In a recent review of cerebral asymmetry and language development, Bishop (2013) argued that before we can grasp the opportunities presented by technological developments in neuroscience and genetics, we need to do basic research to clarify how best to conceptualize and reliably measure cerebral asymmetry.

While twin study may not provide conclusive evidence as to the origins or mechanisms between human handedness and brain development or cognitive process, it indubitably provides an important first step to clarify these problems. It is essential however that neurodevelopmental factors specific to twinnedness be included in the analysis (cf. Gurd et al., 2013; Gurd and Cowell, 2013).

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Differences in cerebral cortical anatomy of left- and right-handers

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The left and right sides of the human brain are specialized for different kinds of information processing, and much of our cognition is lateralized to an extent toward one side or the other. Handedness is a reflection of nervous system lateralization. Roughly ten percent of people are mixed- or left-handed, and they show an elevated rate of reductions or reversals of some cerebral functional asymmetries compared to right-handers. Brain anatomical correlates of left-handedness have also been suggested. However, the relationships of left-handedness to brain structure and function remain far from clear. We carried out a comprehensive analysis of cortical surface area differences between 106 left-handed subjects and 1960 right-handed subjects, measured using an automated method of regional parcellation (FreeSurfer, Destrieux atlas). This is the largest study sample that has so far been used in relation to this issue. No individual cortical region showed an association with left-handedness that survived statistical correction for multiple testing, although there was a nominally significant association with the surface area of a previously implicated region: the left precentral sulcus. Identifying brain structural correlates of handedness may prove useful for genetic studies of cerebral asymmetries, as well as providing new avenues for the study of relations between handedness, cerebral lateralization and cognition.

Keywords: MRI, handedness, cortical surface area, brain asymmetry, FreeSurfer

INTRODUCTION

Handedness is perhaps the most overt reflection of lateralization of the central nervous system in humans. Humans show a strong and population-level bias toward using one hand rather than the other for manual activities, which is unusual among mammals (Vallortigara et al., 2011). Roughly 90% of humans are right-handed, while even other primates (e.g., chimpanzees and macaques) do not show such a strong degree of population-level handedness (Lonsdorf and Hopkins, 2005; Meunier et al., 2013). This motor asymmetry is observable at least as early during human development as 15 weeks of gestation, and is preceded by asymmetries of arm movements even earlier (Hepper, 2013). In addition the tendency toward right handedness has apparently been present throughout human history, and across cultures and continents (Coren and Porac, 1977; Hardyck and Petrinovich, 1977; McManus, 1991, 2009; Faurie and Raymond, 2004).

Due in part perhaps to its minority status and past cultural stigmatization, left-handedness has often been studied in the context of pathology, for example in relation to Alzheimer's disease (de Leon et al., 1986), substance use (London, 1989), and autoimmune disorders (Geschwind and Behan, 1982). Handedness has also been investigated in relationship to lateralized cognitive functions, such as visuospatial processing (Gordon and Kravetz, 1991), face recognition (Luh et al., 1994; Willems et al., 2010; Bukowski et al., 2013) and prominently, language (Tzourio et al., 1998; Knecht et al., 2000b). Knecht and colleagues found an increased incidence of bilateral and right hemisphere language lateralization among left-handers, compared to right-handers, although the majority of left/mixed handers still showed left-hemisphere language dominance (Knecht et al., 2000a,b). This suggests that developmental mechanisms affecting cerebral language dominance overlap to an extent with those influencing hand motor control. However, it remains poorly understood how these different domains of functional lateralization are related to each other (Badzakova-Trajkov et al., 2010).

Several early attempts to understand human handedness attributed right-handedness to socio-cultural, anatomical, as well as genetic factors (for a review see Hardyck and Petrinovich, 1977 or Corballis et al., 2012 for a more recent one). However, the developmental basis of human brain lateralization remains

almost wholly unknown, and likewise the causes of its variation are hardly understood (Willems et al., 2014). One robust observation is that males show a slightly higher proportion of left-handedness than females (Halpern et al., 1998; Peters et al., 2006; Sommer et al., 2008). Recent twin studies, based on thousands of families, have indicated that 21–24% of the liability to left-handedness can be explained by additive genetic effects (Medland et al., 2009; Vuoksimaa et al., 2009). This indicates that genetic variation plays a role in causing variation in handedness. In contrast to original models of handedness as a monogenic trait (Annett, 1985; McManus, 1985), recent evidence from genome-wide association studies strongly suggest more complex models (Medland, 2009; McManus et al., 2013; Armour et al., 2014). So far, studies aimed at discovering the specific genetic loci involved have yielded tentative associations with the genes AR, APOE, COMT, PCSK6, LRRTM1 (Medland et al., 2005; Francks et al., 2007; Savitz et al., 2007; Bloss et al., 2010; Scerri et al., 2011; Brandler et al., 2013). Although originally discovered in populations affected by dyslexia, PCSK6 has also shown association with degree of handedness in a healthy sample of unrelated adults (Arning et al., 2013). It is not yet known how these genes may influence asymmetrical development of the brain (see Ocklenburg et al., 2013).

Identifying brain anatomical correlates of left-handedness may provide potential endophenotypes for further genetic association studies (Ocklenburg et al., 2013; Willems et al., 2014). Finding anatomical correlates of left-handedness may also inform on the relations between handedness and lateralized cognitive functions, and more broadly on brain structure-function relationships (Ocklenburg et al., 2013; Willems et al., 2014). Amunts et al. (1996) found deeper left precentral sulci in right-handers than left-handers using manual segmentations of magnetic resonance (MR) images. Consistent with this, Foundas et al. (1998) examined left-right asymmetries of the precentral gyrus in a sample of 15 left- and 15 right handers based on manual segmentations of their MR images, and found leftward asymmetries in right-handers, but no consistent asymmetry in left-handers (also see Kloppel et al., 2007 and Willems and Hagoort, 2009, for corroborating findings using functional MR imaging). More recently, gray matter volume in the central sulcus was shown to relate to hand motor skill, but to different extents depending on handedness (Herve et al., 2005). In addition, asymmetry of the planum temporale (PT), the posterior portion of the superior surface of the temporal lobe, has been reported to associate with hand preference (Steinmetz et al., 1991; Foundas et al., 1995; Herve et al., 2006). However, results regarding the PT have not been consistent throughout the literature (Witelson and Kigar, 1992; Good et al., 2001). Similarly, an association between handedness and cerebral torque, another structural brain asymmetry, has also been assessed with inconclusive results (Narr et al., 2007). More recently, Powell et al. (2012) in a study of 40 left-handers and 42 right-handers found differences in sulcal shape of the pars orbitalis (PO) and pars triangularis (PTr), as well as differences of volumetric asymmetry within the PO. To our knowledge, Good et al. (2001) has studied the largest sample to have been used in examining brain morphological differences related to handedness. Using a voxel-based morphometry analysis with a total sample of 465 subjects (67 lefthanders) they did not find structural correlates of handedness in the brain. This suggests that any such correlates are subtle and will require larger samples and/or other ways to quantify brain structure, in order to detect them unambiguously.

The goal of the present study was to identify cerebral cortical differences between left and right-handers, by analyzing the largest sample used so far for this purpose (106 left-handed subjects and 1960 right-handed subjects), and using recently developed methodology for the automated segmentation and quantification of regional gray matter (Fischl et al., 2004). We analyzed the data in three stages. First we examined total cortical surface area in relation to handedness. Then, we tested a set of candidate cortical regions for associations with handedness, based on the previous studies mentioned above. Finally, we carried out a screen over all remaining cortical regions.

METHODS

STUDY DATASET

The Brain Imaging Genetics (BIG) study was initiated in 2007 and comprises healthy volunteer subjects, including many university students, who participate in diverse imaging studies at the Donders Centre for Cognitive Neuroimaging (DCCN), Nijmegen, The Netherlands (Franke et al., 2010). At the time of this study the BIG subject-pool consisted of 2337 self-reported healthy individuals (1248 females) who had undergone anatomical (T1-weighted) MRI scans, usually as part of their involvement in diverse smaller-scale studies at the DCCN, and who had given their consent to participate in BIG. Their median age was 23 years. A subset of 235 subjects had undergone a brain MRI scan twice, with at least 1 day separation between scans. Fifty percent of the 235 re-scans took place within 181 days of the first, with the mean elapsed time being 320 days ($SD = 360$). At the time of the first scan, the median age of this group was 23 years.

Handedness of the participants was assessed by an item in their enrolment form. This consisted of subjects selecting the appropriate label, either "left-handed/right-handed" (in Dutch). We discuss the validity of this method of assessing handedness further below. Only those subjects who clearly indicated one or the other state were included in our analysis. This resulted in a sample of 1960 right-handed subjects and 106 left-handed subjects, with a median age of 22 years and a standard deviation of 11 years. The proportion of left-handers was substantially lower than in the general population; this was due to left- handedness being used as an exclusion criterion for some of the imaging studies that were pooled into the overall BIG dataset.

IMAGE ACQUISITION

MRI data in BIG were acquired with either a 1.5 Tesla Siemens Sonata or Avanto scanner or a 3 Tesla Siemens Trio or TimTrio scanner (Siemens Medical Systems, Erlangen, Germany). Given that images were acquired during several smaller scale studies, the parameters used were slight variations of a standard T1-weighted three-dimensional magnetization prepared rapid gradient echo sequence (MPRAGE; $1.0 \times 1.0 \times 1.0$ mm voxel size). The most common variations in the TR/TI/TE/sagittal-slices parameters were the following: 2300/1100/3.03/192, 2730/1000/2.95/176,

2250/850/2.95/176, 2250/850/3.93/176, 2250/850/3.68/176, 2300/1100/3.03/192, 2300/1100/2.92/192, 2300/1100/2.96/192, 2300/1100/2.99/192, 1940/1100/3.93/176 and 1960/1100/4.58/176. There was also variation in the number of headcoils used across BIG scans, however, no systematic differences were observed in their use between left- and right-handed subjects. The following arrays were employed (and their frequencies) in the right-handed population: 32-channel (24%), 12-channel (4%), 8-channel (38%), arrays and single headcoil (33%). In the left-handed population, this distribution was 32-channel (27%), 12-channel (0%), 8-channel (33%), arrays and single headcoil (40%).

IMAGE PROCESSING

Automated parcellation of cerebral cortical regions from T1-weighted images was done in FreeSurfer v5.1 (Fischl et al., 2004) according to the Destrieux atlas (Destrieux et al., 2010) within the "-recon-all" processing pipeline, and using default parameters. Measures of surface area (in mm^2) were produced for the total cortical surface and for each of 74 cortical parcellations, in each hemisphere. Outlier values (more extreme than 3.5 *SD* from the mean) were excluded for each measure. The scan–rescan correlation of each measure was then calculated in the sample of 235 subjects who had undergone two MRI scans, after correcting for the potential covariate effects of age, sex, total cortical surface area and scanner field strength (IBM SPSS v.20).

Out of the 74 covariate-corrected bilateral cortical measures, 23 were excluded from subsequent analyses, due to low scan–rescan correlation in either left, right or both structures (Pearson's $r < 0.7$; i.e., corresponding to shared proportion of variance between scan and re-scan measures of <0.49). Regional measures of cortical thickness were also generated. There is evidence that cortical surface and thickness have independent sources of variation (Panizzon et al., 2009). However, we discarded the thickness measures because the majority (81%) showed scan–rescan correlations below 0.7.

CORTICAL CORRELATES OF HANDEDNESS

We tested for associations between handedness and cortical surface areas using repeated-measures ANOVA, implemented in SPSS (IBM SPSS v.20). Hemisphere (left vs. right) was factored as a within-subjects variable and handedness group as a between-subjects variable in a full factorial design. This allowed the detection of bilateral associations of handedness with cortical surface areas, as well as asymmetrical associations (by means of the interaction between handedness and hemisphere). We first tested the total hemispheric surface areas, and then we tested the regional surface areas. In addition, the following covariates were entered into the analyses: sex, age, scanner field strength, and total (i.e., left plus right) hemispheric surface area (the latter only for the analyses of regional surfaces).

We tested candidate cortical regions motivated by previous findings in the literature (specifically by the studies reviewed in the introduction). We separated these candidate regions into three domains; language, motor control and visual processing. Language-related candidate regions were the inferior frontal gyrus and superior temporal gyrus. These corresponded most closely to the following parcellations within the Destrieux atlas, that had also showed a robust scan–rescan correlation: Opercular part of the inferior frontal gyrus, triangular part of the inferior frontal gyrus, anterior transverse temporal gyrus (of Heschl), lateral aspect of the superior temporal gyrus, and PT. The motor control candidate regions were the superior and inferior parts of the precentral sulcus (as defined in the Destrieux atlas). The visual-related candidate regions comprised inferior and ventral areas of the temporal lobe. In the Destrieux atlas these corresponded most closely to the following regions: inferior temporal gyrus, lateral occipito-temporal gyrus (fusiform gyrus) and lingual part of the medial occipito-temporal gyrus. We applied Bonferroni corrections for the comparisons done within each of these domains.

After the analysis of candidate regions, we then tested all of the remaining cortical regions for differences between left- and right-handers, again using Bonferroni adjustment to correct for multiple testing.

POWER ANALYSIS

We used G∗Power v3.1.9 (Faul et al., 2009) to estimate the necessary effect sizes to be detected given our study design. We considered our sample size, a required power (1-β) of 80%, a correlation between bilateral volumes of $r \sim 0.8$, and an α level corrected for multiple testing. This resulted in estimates of partial $\eta^2 \sim 0.07$ [$F_{(1,\ 2055)} \sim 5.7$] for analyses within each of the candidate domains, and a partial $\eta^2 \sim 0.09$ [$F_{(1,\ 2055)} \sim 10$] for the analysis of the remaining cortical surfaces. In other words we had 80% power to detect an association explaining 9% of the residual variance in a regional cortical surface area after having removed the effects of covariates and after considering the multiple comparisons, for the screening analysis of non-candidate regions.

RESULTS

The proportion of left-handers in our sample differed significantly between males and females. Of the 942 males, 59 were left-handed (6.3%), and of the 1077 females, 47 were left-handed (4.4%); $\chi^2_{(1)} = 4.56$, $p = 0.02$, phi = 0.047.

Handedness did not show a significant association with bilateral hemispheric surface area, nor with overall hemispheric surface asymmetry (see **Tables 1**, **2**). None of the candidate regions, related to either language, visual processing, or motor control showed significant evidence for association with handedness after correction for multiple testing within each of these domains (see **Table 3**). The only regions showing main effects of handedness with $p < 0.05$ before correction for multiple testing were the superior precentral sulcus and the inferior temporal gyrus. Means (and *SD*s) for these regions, by hemisphere and handedness group, are shown in **Table 4**.

Tables 5, **6** show results for the remaining (non-candidate) regional surface areas that reached nominal significance (i.e., uncorrected $p < 0.05$) for an association with handedness, either as a main effect on bilateral surface or as an interaction with hemisphere. None of these associations survived correction for multiple testing. The results for all cortical regions and covariates, regardless of nominal significance, can be found in

Table 1 | Mean surface areas (and *SD*s) for the left and right hemispheres, by handedness.

	Left-handers	Right-handers
Left hemisphere surface area	87855.1 (7717.6)	87984.5 (8469.9)
Right hemisphere surface area	87817.2 (8133.5)	88295.6 (8487.4)

Table 2 | Repeated-measures ANOVA results from testing for an association between handedness and total hemispheric cortical surface areas.

	Repeated-measures ANOVA		
	P	*F*	Partial η^2
Handedness	0.114	2.501	0.001
Handedness ∗ Hemisphere	0.132	2.266	0.001
Sex	<0.001	1193.7	0.367
Age	<0.001	90.1	0.042
Scanner field strength	<0.001	12.48	0.006

Supplementary Material, together with descriptive statistics of all metrics, per handedness group.

DISCUSSION

In a large sample of primarily young adult and healthy individuals, we tested for associations of handedness with total and regional measures of hemispheric cerebral cortical surface area. We report on the largest sample to have been analyzed to date in relation to this question. The proportion of left-handers in our sample was lower than in the general population, due to an exclusion of left-handers from some of the smaller studies that were pooled to create our BIG dataset. This exclusion bias, however, did not affect the heterogeneity of scan parameters present in both handedness groups, as reflected in the similar usage of headcoils between them. Nonetheless, we observed a sex difference in the incidence of left-handedness that was consistent with previous literature (with left-handedness occurring at an elevated rate in males; Sommer et al., 2008).

We did not observe any difference in bilateral cortical surface area in left-handers compared to right-handers. Nor did we find significant evidence for associations of handedness with region-specific bilateral surface areas, or their asymmetries, for regions related to language, hand motor control, or visual processing (Foundas et al., 1998, 1995; Willems et al., 2010). Our data therefore, provide little support for previously reported region-specific associations with handedness, although the Destrieux atlas' definitions of regions might not be identical to the definitions used in these previous studies. For example, the PT in the Destrieux atlas extends parietally (Destrieux et al., 2010), which is not a classic neuroanatomical definition (Geschwind and Levitsky, 1968; Steinmetz et al., 1991).

A limitation of our study was that, due to our large sample size and the number of cortical regions analyzed, systematic manual checking and adjustment of the automated parcellations was not feasible. Visual checks were made for only a small minority of images and not targeted to specific regions. However we exploited our subset of twice-scanned subjects in order to exclude regions that were not consistently parcellated from scan to re-scan, and also used outlier exclusion, as two forms of quality control. Clearly there is a need for improved methods of automated parcellation that capture some of the more variable and anatomically complex cortical regions better, in order to carry out future studies based on thousands of images. Another caveat is that the left and right definitions of cortical regions can only be considered "homologous" on the basis of information that was used in constructing the Destrieux atlas (that included information on cytoarchitecture), but this does not necessarily imply strict homology in genetic/developmental terms.

We found a suggestive association of handedness with the bilateral surface area of the superior part of the precentral sulcus, a region overlapping primary motor cortex. However, this association did not survive correction for multiple testing. Left-handers showed reduced surface areas compared to right handers in our sample (**Table 4**), which is at least consistent with the findings reported by Amunts et al. (1996) and Foundas et al. (1998). Males tend to have larger brains than females, which was also the case in our dataset, but this observed trend of decreased cerebral cortical surface area in left-handers was independent of this sex effect, and in the opposite direction to what might be predicted by it. Another suggestive association was found bilaterally with the inferior temporal gyrus. Again, left-handers in our sample showed reduced surface areas bilaterally (**Table 4**).

Our broader screen of non-candidate regional surface area and asymmetry differences between left- and right-handers did not identify significant novel associations. While relatively large, our sample size allowed us to detect standardized effect sizes regarded as medium (http://imaging.mrc-cbu.cam.ac.uk/statswiki/FAQ/effectSize), both before and after adjustment for multiple comparisons.

Although our dataset included a degree of heterogeneity in terms of scanning parameters used, there was no systematic difference in parameters applied for left- and right-handers, and we only analyzed measurements that showed a high scan–rescan correlation in twice-scanned subjects, despite this heterogeneity. Future studies based on even larger datasets will likely be affected by the same issue of heterogeneity, since large datasets are typically achieved through data pooling from multiple sources. It is therefore, encouraging that most of our measurements showed high scan–rescan correlations regardless of scanning heterogeneity.

An important issue in research on handedness is how exactly to define the trait. Many approaches have been taken to measure hand preference, ranging from motor performance measurements (e.g., relative hand skill, relative grip-strength; see Clerke and Clerke, 2001, for a brief overview); to self-report inventories assessing hand choice across various manual activities (Crovitz and Zener, 1962; Annett, 1967; Oldfield, 1971). Handedness inventories that account for preference across a range of tasks yield a rich assessment of (the degree of) handedness, and a detailed picture of its inter-subject variability. However, the resulting data are usually bimodal and are often subsequently dichotomized. For example, (Tan, 1993) showed

Table 3 | Summarized results for the candidate cortical regions.

		Repeated-measures ANOVA		
		P	***F***	**Partial η^2**
LANGUAGE-RELATED				
Opercular part of the interiorfrontal gyrus	Handedness	0.73	0.12	<0.001
	Handedness ∗ Hemisphere	0.63	0.23	<0.001
Triangular part of the inferior frontal gyrus	Handedness	0.88	0.02	<0.001
	Handedness ∗ Hemisphere	0.17	1.8	0.001
Anterior transverse temporal gyrus (of Heschl)	Handedness	0.86	0.03	<0.001
	Handedness ∗ Hemisphere	0.06	3.4	0.002
Lateral aspect of the superior temporal gyrus	Handedness	0.57	0.33	<0.001
	Handedness ∗ Hemisphere	0.36	0.85	<0.001
Planum temporale	Handedness	0.42	0.64	<0.001
	Handedness ∗ Hemisphere	0.94	0.01	<0.001
MOTOR CONTROL-RELATED				
Superior part of the precentral sulcus	Handedness	0.044	4.07	0.002
	Handedness ∗ Hemisphere	0.6	0.28	<0.001
Inferior part of the precentral sulcus	Handedness	0.76	0.09	<0.001
	Handedness ∗ Hemisphere	0.85	0.03	<0.001
VISUAL-RELATED				
Inferior temporal gyrus	Handedness	0.037	4.36	0.002
	Handedness ∗ Hemisphere	0.58	0.3	<0.001
Lateral occipito-temporal gyrus (fusiform gyrus)	Handedness	0.17	1.87	0.001
	Handedness ∗ Hemisphere	0.53	0.4	<0.001
Lingual part of the medial occipito-temporal gyrus	Handedness	0.26	1.27	0.001
	Handedness ∗ Hemisphere	0.1	2.67	0.001

Reported are p-values before correction for multiple testing (none survived this correction).

Table 4 | Means (and *SD*s) for the superior part of the precentral sulcus, and inferior temporal gyrus, by hemisphere and handedness group.

	Left hemisphere		Right hemisphere	
	Left-handers	**Right-handers**	**Left-handers**	**Right-handers**
Superior part of the precentral sulcus	914.9 (207.5)	952.7 (200.9)	965.1 (201.9)	990.4 (214.8)
Inferior temporal gyrus	1853.2 (328.6)	1911.7 (311.3)	1744.8 (319.6)	1787.6 (281.8)

that hand preference, when assessed by a very detailed questionnaire (Waterloo handedness questionnaire; Steenhuis and Bryden, 1989), shows a clear distinction between left-handed and right-handed populations. Further evidence for an intrinsic dichotomy in handedness was also provided by McManus (1991) who observed the same proportion of left-handers regardless of the questionnaire used. Accordingly, simple self-assessments of overall handedness, such as that used in the present study (asking subjects only to categorize themselves as left- or right-handed) show close agreement with dichotomous scoring of handedness as derived from multi-item inventories, as well as robust test–retest repeatability (Bryden et al., 1991; Tan, 1993; Ransil and Schachter, 1994). We are therefore confident of the validity of the binary, self-reported assessment of handedness that was used in our study.

Identifying cortical regional correlates of handedness may prove particularly useful in providing endophenotypes for future genetic studies of this trait, as well as clarifying the relationships between this and other forms of cerebral lateralization (Ocklenburg et al., 2013; Willems et al., 2014). We note that an association between handedness and cerebral cortical anatomy does not necessarily imply a simple causative relationship between the two. While it is conceivable that hand preference may arise due to hemispheric differences in cortical anatomy and function, it is equally conceivable that hand preference exerts developmental effects on cerebral cortical anatomy and function.

Table 5 | Summary results for non-candidate cortical regions that achieved nominal significance in ANOVA.

Cortical surface areas		Repeated-measures ANOVA		
		P	***F***	**Partial η^2**
Anterior part of the cingulate gyrus and sulcus (ACC)	Handedness	0.139	2.19	0.001
	Handedness ∗ Hemisphere	0.023	5.18	0.003
Middle-anterior part of the cingulate gyrus and sulcus (aMCC)	Handedness	0.67	0.18	<0.001
	Handedness ∗ Hemisphere	0.003	8.99	0.005
Superior occipital gyrus (O1)	Handedness	0.04	4.23	0.002
	Handedness ∗ Hemisphere	0.255	1.3	<0.001
Posterior transverse collateral sulcus	Handedness	0.648	0.21	<0.001
	Handedness ∗ Hemisphere	0.048	3.92	0.002
Superior frontal sulcus	Handedness	0.038	4.31	0.002
	Handedness ∗ Hemisphere	0.221	1.5	<0.001
Sulcus intermedius primus (of Jensen)	Handedness	0.743	0.14	<0.001
	Handedness ∗ Hemisphere	0.037	4.37	0.002
Parieto-occipital sulcus (or fissure)	Handedness	0.029	4.8	0.002
	Handedness ∗ Hemisphere	0.25	1.32	<0.001

None of these results survived correction for multiple testing. Complete results for all regions and covariates are in Supplementary Table 1.

Table 6 | Means (and *SD*s) for non-candidate cortical regions that achieved nominal significance in ANOVA, by hemisphere and handedness group.

	Left hemisphere		Right hemisphere	
	Left-handers	**Right-handers**	**Left-handers**	**Right-handers**
Anterior part of the cingulate gyrus and sulcus (ACC)	1648.0 (223.2)	1707.4 (264.5)	1998.8 (251.3)	2016.7 (271.1)
Middle-anterior part of the cingulate gyrus and sulcus	974.6 (144.7)	1014.5 (170.3)	1144.0 (162.7)	1114.1 (169.8)
Superior occipital gyrus (O1)	1131.5 (166.2)	1101.1 (167.7)	1251.1 (177.8)	1239.6 (186.7)
Posterior transverse collateral sulcus	300.7 (70.9)	294.2 (66.4)	373.0 (98.8)	386.9 (98.8)
Superior frontal sulcus	2004.9 (286.8)	2077.1 (302.7)	1867.6 (271.7)	1906.7 (296.1)
Sulcus intermedius primus (of Jensen)	280.2 (145.6)	257.6 (127.3)	350.1 (150.3)	364.0 (151.7)
Parieto-occipital sulcus (or fissure)	1445.9 (225.9)	1429.0 (239.3)	1584.5 (265.8)	1544.2 (255.8)

As noted in the Introduction, there is strong evidence indicating that motor asymmetry of the arms and hands is initiated very early during human embryonic development, possibly even before the cerebral cortex exerts significant influence (Hepper, 2013). These early motor asymmetries, potentially under spinomuscular control, could therefore contribute to the determination of both handedness and regional cortical development.

Left-handed people show increased rates of reductions or reversals of lateralized brain functions, compared to right-handers (reviewed by Willems et al., 2014). Functional imaging studies of left-handers allow the possibility to study not only basic lateralization of brain function (e.g., of face perception), but also embodied cognition, and the extent of co-lateralization of different cognitive functions (Willems et al., 2014). Our survey of cerebral anatomical correlates of handedness may serve to inform these investigations, as it can suggest a prioritization of specific regions and cognitive processes to focus on with functional imaging techniques.

It is clear from our results, and those of previous studies, that any changes in brain structure associated with left-handedness are subtle. As noted earlier, it is likely that the genetic contributions to left-handedness are heterogeneous in nature, with multiple different genes being involved, and the same may be true of environmental influences (which also remain poorly understood). Etiologic heterogeneity suggests that there will be different forms of left-handedness which may manifest differently in terms of how striking any brain structural and functional correlates may be, and also differently in how, and to what extent, other lateralized cognitive systems are re-organized. A promising approach for studying the relations between lateralization and cognition will therefore be to specifically recruit left-handers, in order to recruit sufficient numbers for characterizing their heterogeneity, followed by assessments of brain structure and function in addition to neuropsychological testing, and genetic analysis (Marie et al., 2013; Mellet et al., 2013).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.00261/abstract

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Quantifying cerebral asymmetries for language in dextrals and adextrals with random-effects meta analysis

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Speech and language-related functions tend to depend on the left hemisphere more than the right in most right-handed (dextral) participants. This relationship is less clear in non-right handed (adextral) people, resulting in surprisingly polarized opinion on whether or not they are as lateralized as right handers. The present analysis investigates this issue by largely ignoring methodological differences between the different neuroscientific approaches to language lateralization, as well as discrepancies in how dextral and adextral participants were recruited or defined. Here we evaluate the tendency for dextrals to be more left hemisphere dominant than adextrals, using random effects meta analyses. In spite of several limitations, including sample size (in the adextrals in particular), missing details on proportions of groups who show directional effects in many experiments, and so on, the different paradigms all point to proportionally increased left hemispheric dominance in the dextrals. These results are analyzed in light of the theoretical importance of these subtle differences for understanding the cognitive neuroscience of language, as well as the unusual asymmetry in most adextrals.

Keywords: cerebral asymmetries, language, handedness, WADA test, laterality

GENERAL INTRODUCTION

The curious relationship between language-related asymmetries in the human brain and handedness was a fundamental question for neuropsychological and behavioral neuroscience over almost all of the twentieth century. Sadly, this question has become of more specialist interest in the last 20 years or so, as paradigms in the cognitive neuroscience of language become increasing less focused on questions related to the left and the right cerebral hemispheres. In parallel, during the 1970s and 1980s handedness researchers gradually became embroiled in methodological arguments over issues such as preference vs. performance, the precise definition of adextrality, and how measures of hemispheric specialization interact with fashionable covariates such as handwriting posture, sex, familial sinistrality, and so on. Because the relationship between handedness and language laterality is subtle (e.g., Baynes and Long, 2007), statistical differences between right handers and non-right handers are not always obtained, leading some scientists to conclude that these groups are effectively homogeneous with respect to cerebral asymmetry. Many studies, (in functional magnetic resonance imaging [fMRI] in particular), have avoided any controversy (or, theoretically, unnecessary additional variance) by restricting analysis to dextrals (e.g., Berlin et al., 1973; Lindell and Nicholls, 2003; Voyer and Ingram, 2005; Hirnstein et al., 2010). In others, differences between dextrals and adextrals are **examined**, but the results are often inconclusive about real differences. Tzourio-Mazoyer et al. (2014) report some subtle anatomical differences between dextrals and adextrals, but find no functional activation contrasts in a large sample. Szaflarski et al. (2012) find that adextral children are 85% left brain dominant for language, hardly less than the dextral sample using their methods. Van der Hagen and colleagues argue that the effects of handedness on cerebral asymmetry are small, and suggest using direct measures of lateralization obtained from fMRI (see Van der Haegen et al., 2013b; also see Brysbaert, 1994).

This paper will attempt to reconcile evidence from several sources that all speak to the puzzling relationship between language dominance and dominant hand (particularly in the non-right handed, "adextral" population). In particular, we want to establish up to date estimates of any differences between dextrals and adextrals, comparing fMRI and other modern neuroscientific methods of the late twentieth and twenty-first centuries with the well-worn techniques of WADA testing, dichotic listening and visual half field experiments which dominated earlier in the twentieth century. To this end, we use meta analysis to try and establish whether there is a consistent difference between dextrals and adextrals, and if so, what is the best estimate for its magnitude, on average.

Several challenges are common across the diverse methods which examine language lateralization in individual people. Even within the specific paradigms outlined below, many studies differ in task, the reliability of the measurements, and the inclusion criteria for each group, in particular for the adextral sample. Within task, there is now some evidence to show that different strategies that individuals use can dramatically affect laterality quotients (for example, attentional biases/strategies may, and often do, muddy measurement of perceptual bias in dichotic listening experiments; Hugdahl and Andersson, 1986; Hugdahl et al., 2008; Hiscock and Kinsbourne, 2011). These direct attention blocks have also become very popular for experiments which help identify the relative contributions of bottom up and top

down processes in auditory perception (Hirnstein et al., 2013; Passow et al., 2014).

Nevertheless, some of these concerns about between-study differences are less crucial if the data are treated meta-analytically. If some moderating variable, like sex or familial left handedness (Bishop, 1990), for example, is not balanced across two studies, differences in lateralization obtained may depend to an unknown degree on that unmeasured covariate. This sort of problem is lessened quite dramatically by an approach which produces a central tendency, rate ratio or effect size across many experiments (where presumably the distribution of the potential covariates will average out as simply another source of noise). In some sense, a multitude of studies which are heterogeneous, yet in spite of their differences, tend to point in the same direction when viewed collectively, is a strength rather than a weakness from a meta-analytic perspective.

Our working hypothesis for this set of studies is that all of the paradigms meta analyzed below will produce crudely equivalent group differences in proportions of left hemispheric speech/language dominance of approximately 15–20%, favoring the dextral samples. For researchers interested in handedness, such a result would come as no surprise (Willems et al., 2014). Other scientists are less concerned about differences between dextral and adextral people (as the majority of both groups share direction of cerebral dominance, on average) or argue that handedness and cerebral dominance may be confounded with one another (Hervé et al., 2013). Perspective of the researcher may be relevant here: for an electrophysiologist studying a language-related waveform, exclusion of adextrals may be unnecessary for two reasons: adextrals are rare, (typically representing roughly 10% of the population), and in any case, most of them will be lateralized in a fashion similar to dextrals. Nevertheless, for many neuropsychologists, the relationship between handedness and cerebral asymmetry is real and needs explaining. In some sense, it is ironic that interest in handedness and asymmetry has waned as newer techniques (that the neuropsychologists of the 1970s could not have dreamed of) have been developed. Our goal in this paper is to help establish the most accurate estimates, on average, for left hemispheric dominance in dextrals and adextrals, and to suggest why these proportions are important for providing fresh impetus to this field.

GENERAL MATERIALS AND METHODS

Each of the paradigms/domains described below were systematically searched for papers that included estimates related to speech and language asymmetry for samples of dextral and adextral participants. Potential studies were selected from computerized databases (ScienceDirect, PubMed) and Google Scholar searches, as well as from the reference lists of all papers collected previously which met the inclusion criteria. We also relied quite heavily on related reference and cited reference searches. A few sources published in non-English languages were perused by colleagues for the relevant frequency data. In order to be included in the analysis, each study must have included dextral and adextral participants, and provided frequency data for those two groups on the dependent measures(s) related to cerebral asymmetry for language.

A "proportion" approach to the meta analytic procedures has been adopted, using frequency data for dextrals and adextrals rather than the more typical effect size measurements of differences in central tendency. A few papers using this latter kind of meta analysis have been conducted previously (language laterality and handedness: Kim, 1994; sex differences in handedness: Papadatou-Pastou et al., 2008). Such endeavors are useful in trying to establish whether there is a significant difference between dextrals and adextrals (or men and women) on a particular measure, but estimating average effect sizes of this sort cannot be unambiguously converted to estimates of *incidences* in groups of interest. Of course, groups may differ quite dramatically on some measure of central tendency, but the means and variances associated with those differences cannot unambiguously reveal *how many* individuals in each group showed a particular effect. These sorts of issues are explored in much more detail in the growing literature on individual differences, which tends to be rather critical about psychology's obsession with central tendency; see Kanai and Rees (2011), Vogel and Awh (2008), for some of the discussion.

In the particular case of hemispheric specialization, larger average asymmetries favoring dextrals are assumed to be due to a small number of the adextrals in the sample who are lateralized in the opposite direction (i.e., to the other hemisphere). Reduced asymmetries in many or all of the individuals in an adextral sample would require a rather different interpretation. In fact, comparing different measures of a hypothetical underlying construct will be facilitated if the proportions of each group showing a typical pattern are reported. This approach may also circumvent some of the difficulties with test-retest reliabilities of some measures of language-related asymmetry such as dichotic listening (see General Discussion).

One particular difficulty in comparing the different studies summarized in the meta analyses of this paper is that many of them use quite distinct criteria for assigning individuals to operationally-defined dominance groups. For example, many (but not all) studies opt for a "bilateral" or "no difference" category when measured asymmetries between visual fields in tachistiscopic tasks, ears in dichotic listening tasks, or hemispheres in the case of fMRI, do not exceed a pre-specified threshold of lateralization (discussed in Jansen et al., 2006; Seghier, 2008). This problem is circumvented here by grouping together bilateral and no difference groups with those who display asymmetries favoring the right hemisphere on a language task[1].

All meta analyses were performed using MetaXL, developed by Barendregt and colleagues, available as freeware from http://www.epigear.com/index_files/metaxl.html.

For all the analyses *a rate ratio* meta analysis was used (these are referred to as *risk* ratios in some studies, including Experiment 1 on aphasia incidence). These compare the proportion of people in one binomial category to those in the other, and compare

[1]We have used the term "anomalous dominance" here for right brain dominance, bilateral or no dominance categories in any particular study. The term is not intended to presuppose that non-left dominance is somehow pathological, as implied by the "Geschwind-Behan-Galaburda" model of the 1970s (see Bryden et al., 1994; Dellatolas, 1994, for detailed discussion).

this proportion in two separate groups. Statistically, odds ratios, rather than rate ratios, have more attractive mathematical properties for this kind of analysis, such as symmetry about "no difference" in an effect. However, for the frequency data for all the techniques described below, there was no theoretical reason to suspect any differences in the "other" direction—e.g., adextrals being more susceptible to aphasia after left lesions than dextrals; more adextrals with right ear advantages, etc. Finally, rate ratios are easier to interpret.

All available studies for each paradigm were subjected to a random effects meta analysis (using the variance estimators recommended by DerSimonian and Laird, 1986). These techniques allow for statistical estimates of central tendency (as effect sizes, means, rate ratios and so on) and variability to be made across a number of different studies which examine *similar* dependent and independent measures. Fixed effects models assume that each individual study is sampling *the same* underlying population effect and that *all* variance from study to study is measurement noise, sampling error, subtle differences in test administration and so on. Random effects do not assume that all of the underlying studies sample an identical population effect (Haddock et al., 1998; Borenstein et al., 2010; Cumming, 2012); hence there are sources of variation (say, aphasia as classified by different measures in samples tested at slightly different times after the neurological insult, etc.), which will not be identical from study to study. One limitation of random effects methods, however, is that studies with smaller sample sizes can contribute more to the overall effect estimate, as they contribute more to estimates of between study variability—in fixed effects models smaller variances result in larger weights). Nevertheless, the rate ratios from fixed and random effects models will be very similar when the heterogeneity is small, so we favor the more conservative approach of random effects.

For the subsequent paradigm-specific meta analyses, differences in precise tasks used, sex of group members, cut-off procedures, how adextrals were recruited, sampling bias and so on, make it quite clear that a random effects analysis is appropriate. Having said that, these studies are all attempting to estimate, directly or indirectly, differences in hemispheric specialization related to language processing. Studies too numerous to mention have identified the non-perfect relationships between these different techniques (and at times some rather limited test-retest reliabilities) so will not be discussed further (but see Bryden, 1982; Brysbaert, 1994; Binder, 2011 for further discussion of many of the most pertinent issues).

META ANALYSIS 1: APHASIA INCIDENCE AFTER UNILATERAL BRAIN DAMAGE

INTRODUCTION

Most of the early research which addressed language lateralization and handedness depended on studies of aphasic disturbances in individuals (Critchley, 1954). Early attempts to link *right* hemispheric language lateralization to left hand preference for writing (lumped together, erroneously, in fact, as "Broca's rule" e.g., Eling, 1984; Harris, 1991) were discredited quite quickly in the late nineteenth and early twentieth century (Harris, 1991). Case studies, too numerous to review here, have documented examples of "crossed" aphasia and apraxia in single individuals (e.g., aphasia or apraxia after a right hemisphere lesion in a right hander or, much more rarely described, the left hemisphere in a left hander; reviewed in Alexander and Annett, 1996; Coppens et al., 2002). As important as these single cases studies were, it was the large sample studies of aphasia and handedness that debunked the idea of a perfect link between hand preference and a speech-dominant contralateral hemisphere.

These rather laborious group studies of hospital patients with and without aphasia were the first datasets that suggested that right hemispheric dominance in adextrals was not the norm by any stretch of the imagination. Unfortunately, the accuracy of estimates from this research is complicated by the anti-sinistral biases that were common, even in Western cultures, for anyone born prior to World War 2. Inevitably, some proportion of left-handed writers will have been forced to switch their handedness at an early age. Similarly, "left handers" in such cohorts were probably those individuals most resistant to direct or indirect pressures to switch to the preferred right hand (this topic is reviewed in Siebner et al., 2002; Searleman and Porac, 2003) Considering the average age of many stroke patients, these sources of bias will have had persisting effects well into the twentieth century. Unfortunately, dissipation of such effects is happening too late, as such large sample studies have become more expensive and less fashionable. In some of the early experiments, heroic efforts were made to document cases of handedness switch in some "right" handers (e.g., Gloning, 1977), but these were the exception rather than the norm.

For inclusion in this analysis, three criteria needed to be met. First, aphasia incidence needed to be estimated in groups of dextrals and adextrals using the same tests and criteria. Second, the number or proportion of dextrals and adextrals who were so diagnosed out of larger samples of unilateral brain damage was reported. Finally, we expected no admission or strong suggestion of pre-selection of non-right handers in any way that would bias estimates of aphasia frequency after left or right brain damage (see below).

METHODS

Literature searches in Pubmed revealed 1100 sources when "aphasia" and "handedness" were searched for (September, 2014). Many of these studies: (1) only provide the mean handedness of an exclusively dextral sample; (2) are single case reports; and (3) compare treatments of right and left handed dysphasics. Additional potential studies were sourced by cited reference searches of early papers on aphasia in adextrals including Basso et al. (1989, 1990), Brain (1945), Critchley (1954), Goodglass and Quadfasel (1954), Humphrey and Zangwill (1952), Zangwill (1960).

Unfortunately, several large scale studies of aphasia incidence do not report handedness (e.g., Laska et al., 2001; Chilosi et al., 2005) or do not report their data by side of lesion and handedness, as well as by presence or absence of aphasia (e.g., Bingley, 1958; Zangwill, 1960; Brown and Hécaen, 1976; Hécaen, 1976; Vargha-Khadem et al., 1985; Basso et al., 1990; Pedersen et al., 1995, 2004; Basso and Rusconi, 1998; Godefroy et al., 2002). For example they may report how many aphasics in a subgroup

were right or left handed, but these sorts of data are not sufficient, without information about how many patients with left or right unilateral lesions *were not aphasic*. An additional restriction in this literature is that it has gradually shifted into looking for functional evidence for compensation in dysphasics within a damaged hemisphere or in the contralateral (presumably innately non-dominant) hemisphere. These newer studies often have small samples, and examine right-handed patients only which almost inevitably means lesions of the left hemisphere (e.g., Pettit and Noll, 1979; Heiss et al., 1999; Duffau et al., 2003; Krieg et al., 2013).

An additional methodological concern (as if there aren't enough already) in studies of aphasia incidence and handedness is that the earliest (and best cited) papers are not, in fact, composed of samples of *unselected* dextrals and adextrals with unilateral brain damage. Instead they are typically "compilations of scattered individual cases" (Kimura, 1983), where non-right handers were particularly noteworthy when they presented *with* aphasia, and *not so noteworthy when they did not*. For this reason one of the best known studies (Goodglass and Quadfasel, 1954) has been excluded from the analyses. In other experiments, inclusion criteria for individual patients included "adequate tests for aphasia" (Humphrey and Zangwill, 1952), which as Kimura (1983) notes, implies that some dextral and or adextral patients were not routinely tested. We have excluded this source as well.

Studies of unselected series of left and right brain damaged patients, which also recorded handedness are remarkably rare. As Kimura (1983) reports in one of the most cogent analyses, some selectivity (not necessarily described in the manuscript or book) of adextral cases is the norm rather than the exception (see also Annett, 1975, 2002). Nevertheless, we managed to identify 14 such studies, which are the subject matter of the first two meta analyses.

RESULTS

The 14 studies of patients with left brain damage summarized included 2421 dextral and 390 adextral patients; the 13 studies[2] of patients with right brain damage summarized included 1907 dextral and 256 adextral patients. The results of this analysis on aphasia incidence are plotted in **Figure 1**. (Supplementary Material contain the excel spreadsheets for this analysis, which provide the raw frequencies for dextrals and adextrals, the weights of each study in the final rate ratio estimate, and so on). In the top panel, the effects of unilateral *left* hemisphere lesions are depicted, comparing risk ratios calculated for dextral and adextral patients (in that order). A risk ratio in this context contrasts the number of unilateral brain damaged patients with aphasia to those without aphasia; this proportion in dextrals serves as the numerator to the same proportion in adextrals (therefore risk ratios greater than one indicate greater sensitivity in dextrals).

The associated Q statistic (62.52, $p < 0.001$) for aphasia after left brain damage suggests considerable heterogeneity across studies (which validates the use of a random, rather than a fixed-effects analytical strategy). I^2, another measure, provides the percentage of total variance due to variation between studies. The pooled risk ratio suggests that there are no differences between dextrals and adextrals in terms of their susceptibility to aphasia after unilateral left hemisphere lesions: risk of 1.03 (95% C.I. = 0.83–1.27). These same data were heterogeneous across study ($I^2 = 79.21$).

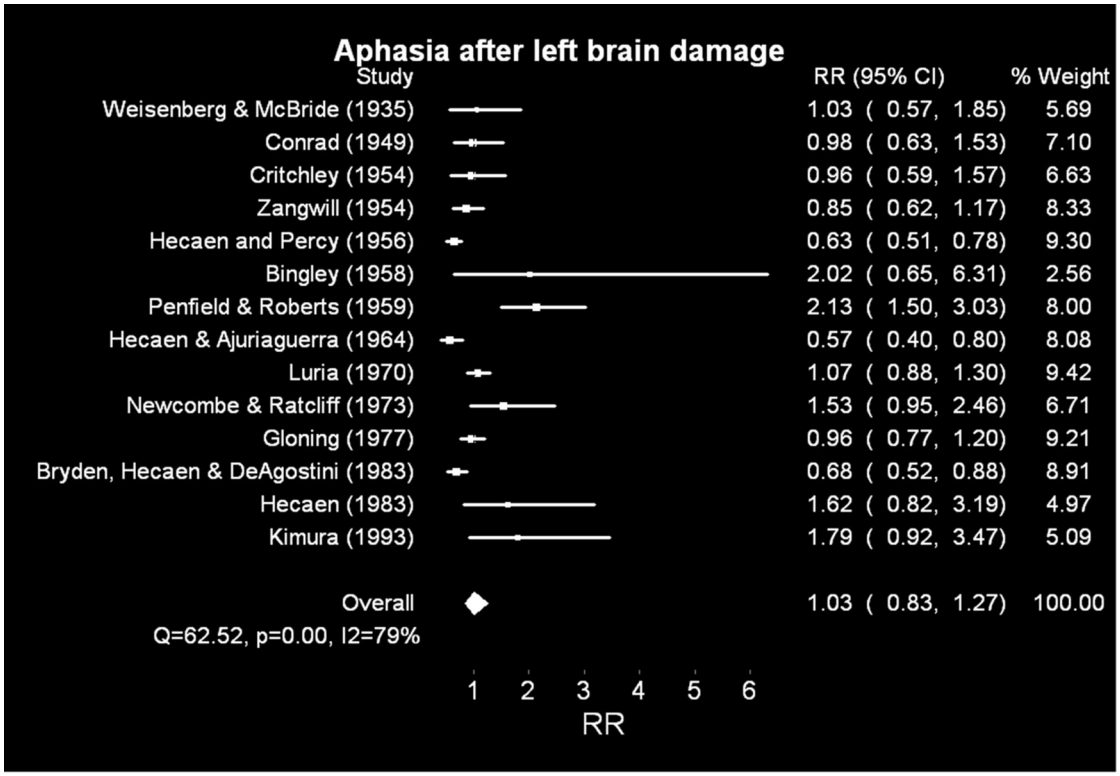
By contrast, the pooled risk ratio following right hemisphere lesions suggests a clear difference (bottom panel), although a considerably noisy one: odds of 0.15 (95% C.I. 0.05–0.44; $I^2 = 92.31$) were obtained one. Stated in terms of *adextral relative to dextral* susceptibility, the risk ratio is 6.7 for adextrals to become dysphasic after a right hemisphere lesion relative to the dextral population. As with the left brain damage analysis above, perhaps unsurprisingly, heterogeneity of these estimates is large: $Q = 156.02$, $p < 0.001$. Many studies not included in the meta analysis quantify aphasia incidence in dextrals after left or right hemispheric damage. These studies result in a similar bias toward greater aphasia incidence after left hemisphere lesions (e.g., McGlone, 1977; Wade et al., 1986).

DISCUSSION

The noisiness of both of these overall effects is partly due to the sample sizes available, for the adextral patients in particular (e.g., adextral n's range for left lesions from 6 to 87; Supplementary Material; for right lesions from 2 to 53; Supplementary Material). Annett (1975, 2002) argues that the series also have different *proportions* of left handers, which shows different inclusion criteria, which will lead to different distributions of speech lateralization. In spite of this heterogeneity, these data suggest that dextrals and adextrals are similarly prone to aphasia after left hemisphere lesions, and that right hemisphere lesions are much more likely to produce dysphasia of some sort in adextrals compared to dextrals. It is tempting to relate the similarity of the two handedness groups in susceptibility to dysphasia after left lesions to statistical noise plus the considerable evidence suggesting that adextrals are *largely* left brained for language, as are the dextrals, of course. Nevertheless, the lack of even a small difference favoring increased incidence in the dextrals is puzzling. Sample size clearly is at issue here, but the samples for the second meta analysis (patients with right brain damage) are similarly limited. The absence of aphasic symptoms in people with left hemisphere damage might mean that they don't present to neurologists or stroke specialists who compile some of these group studies (Levy, 1974; Annett, 2002)—perhaps more of an issue for adextrals after left hemisphere lesions (relative to dextrals), but such selectivity could also affect incidence estimates for aphasia in dextrals after right lesions.

Nevertheless, this meta analysis does suggest that dextrals and adextrals do not differ in terms of susceptibility to aphasia after left hemispheric lesion. Few of the investigators of the original studies have commented on this particular *symmetry*. In part, the absence of a difference in many of the papers was interpreted in terms of *refuting* "Broca's rule"—what was noteworthy at the time was that the adextrals *were not right brained* for language. Comment on their striking similarity to dextrals is infrequent.

[2]The precise numbers of dextral and adextral patients screened after right brain damage were not available in Luria (1970), hence its exclusion from the second but not the first analysis.



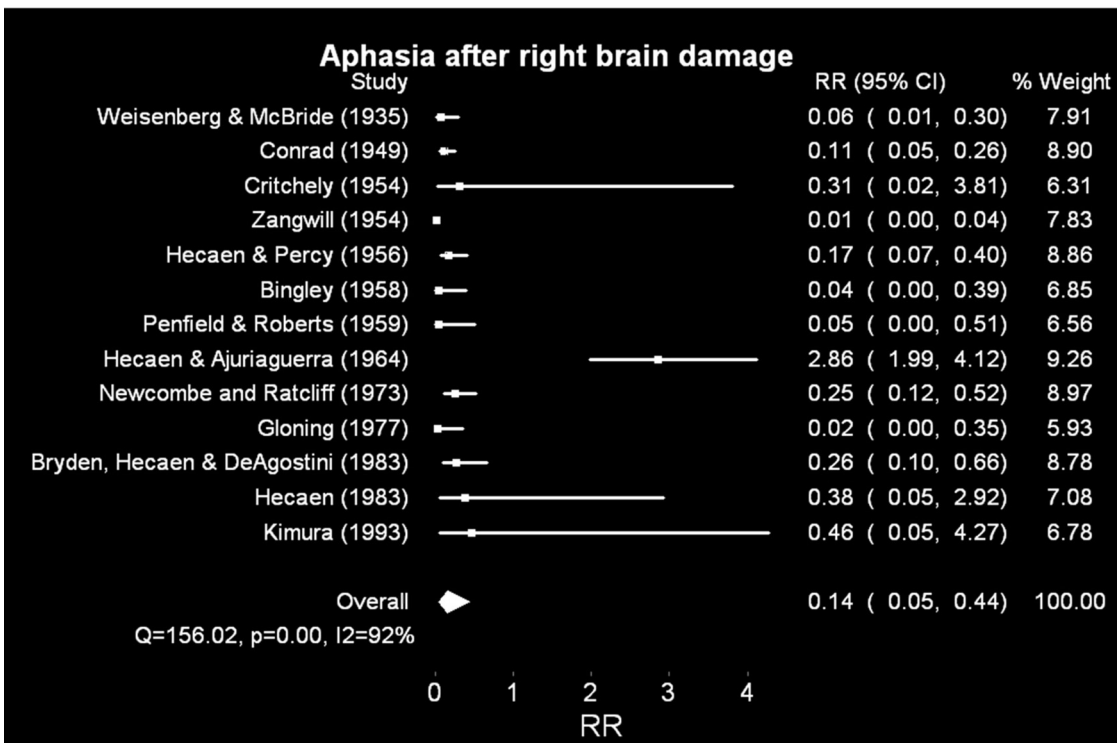


FIGURE 1 | Random effects meta analyses of relative risk of aphasia after unilateral brain damage, dextrals compared to adextrals. Risk ratios greater than one suggest greater susceptibility of dextrals than adextrals; less than one greater susceptibility of adextrals than dextrals. *CI* = 95% confidence intervals. I^2 is a measure of the percentage of total variation due to variation between studies. Note that no estimates of susceptibility were provided in Luria (1970) for right hemisphere lesions. **Top panel**: unilateral left brain damage. **Bottom panel**: unilateral right brain damage. For additional comments and the raw frequencies, for all figures, see Supplementary Materials.

As an aside, some of these early aphasia studies also suggested two parallel but slightly counterintuitive hypotheses about aphasic syndromes in non-right handers. First, Chesher (1936) and Gloning et al. (1969) provided early evidence to show that adextrals were more likely to have dysphasia after brain damage than dextrals (see also Hécaen and Percy, 1956; Satz et al., 1965; Satz, 1979; although Newcombe and Ratcliff, 1973; Kimura, 1983; contest these claims). Second, comparing prognosis in right and non-right handers after becoming dysphasic, the adextrals tend to recover somewhat earlier and more completely (Subirana, 1969; although this claim is also contentious, see Pedersen et al., 1995). These somewhat contradictory findings are in part more understandable (at least) when data from large scale studies of another group of patients began appearing in the 1960s and ideas of *bilateral speech* representation, in adextrals at least, became more commonly understood. It is also tempting to relate the first claim to the current findings; similar dysphasia risk after left lesions but increased risk after right lesions.

META ANALYSIS 2: WADA TESTING IN PRE-SURGICAL EPILEPTIC PATIENTS

INTRODUCTION

Another class of neuropsychological data, distinct from the laborious large sample aphasia incidence studies, has come to dominate thinking about language lateralization and handedness (and unlike the aphasia studies, such experiments continue to be performed to this day). Juhn Wada popularized a technique for determining language lateralisation in pre-surgical candidates for epilepsy surgery (Snyder and Harris, 1997; Wada, 1997). A great advantage of anesthetizing each hemisphere in turn and testing for speech arrest is that participants could be classified trichotomously (left hemisphere dominant; right hemisphere dominant, or bilateral). Bilateral classification was a consequence of either no speech arrest after amytal to either hemisphere (a type one of us refers to students as "good bilateral") or speech arrest after amytal to either hemisphere ("bad bilateral"). Some researchers claim that speech arrest in these later cases can be somewhat less severe than what is typically obtained from patients with epilepsy with more straightforward unilateral speech dominance.

In any case, this technique, in the capable hands of Milner, Rasmussen, Penfield and others at the Montreal Neurological Institute, led to the most popular estimates of speech lateralization in dextrals and adextrals (see **Table 1**). This popularity is somewhat surprising, as of course, most people with intractable epilepsy would have had brains that had dealt with congenital abnormalities for a lifetime; perhaps not the most representative sample for asymmetry estimation in the neurologically-intact brain[3].

Since these early observations, large scale studies using the WADA test have been published on several occasions. The availability of these large n datasets is made possible by the tremendous popularity of the technique in neurosurgery units, even after fMRI availability had become widespread (Baxendale et al., 2008; Wagner et al., 2012). These studies, often with more refined techniques and definitions, are subject to the caveat of potentially abnormal hemispheric lateralization in people with congenital brain abnormalities (Kimura, 1993; Annett, 2002). Nevertheless, the estimates for the most part are largely consistent with the Rasmussen and Milner percentages presented in **Table 1**. Literature searches revealed 350 (partially overlapping) sources when ("WADA" or "IAT" or "sodium amytal") and "handedness" were searched for in PubMed (September, 2014). Additional potential studies were sourced by cited reference searches of early papers on WADA and handedness including Binder et al. (1996), Rasmussen and Milner (1977), Woods et al. (1988) or came up in our other PubMed and Google scholar searches.

Table 1 | Trichotomous classification of speech and language dominance in 266 epileptic patients using the WADA test (Rasmussen and Milner, 1977).

	Speech lateralization		
	Left hemisphere (%)	Bilateral (%)	Right hemisphere (%)
GROUP			
Dextrals	96	0	4
Adextrals	70	15	15

RESULTS

The 32 studies summarized included 2771 dextral and 738 adextral patients. The results of the random effects meta analysis of these studies appears in **Figure 2**. Supplementary Material contains the associated Excel file with the raw data, weights for each study and a description on a separate sheet of some of the studies checked but not included in the analysis. In this comparison, unlike in the aphasia incidence meta analyses above, dextrals and adextrals are compared in one analysis, which contrasts the risk ratios (in this case some investigators would refer to it as a rate ratio) of *left brain dominance* relative to *anomalous dominance* for speech. In this latter category, in the studies where bilateral dominance was occasionally assigned, these cases were pooled with right brain dominance (this convention is also followed in **Figures 3**, **4** for the dichotic listening [DL]/visual half field [VHF] data and the fMRI/ECT/TDS data, respectively).

These data, collectively, contain less heterogeneity across studies ($Q = 43.54$, $p < 0.07$ NS; $I^2 = 28.81\%$) than the aphasia meta analyses above. The rate ratios for 30/32 studies are greater than 1 (range 0.93–3.00). The overall rate ratio is 1.36 (95% CI 1.26–1.46). These data suggest that left brain dominance, at least in epileptic patients selected for and assessed using the WADA test, is more common in dextral populations than adextral ones.

We also modeled % left dominance in the two groups by weighting each group percentage (n left dominant/n left dominant + n anomalous dominance * 100) by the meta-analytically derived inverse weighting (See "weighted means" columns in Supplementary Materials). This procedure suggests a best estimate, on average, of left brain dominance in dextrals of 87% and

[3]For reviews of neural plasticity as a function of age, see Dennis (2000). Early left hemispherectomy often results in right hemispheric language dominance, which in many ways resembles the typical functional organization of language in the left hemisphere (Staudt et al., 2002).

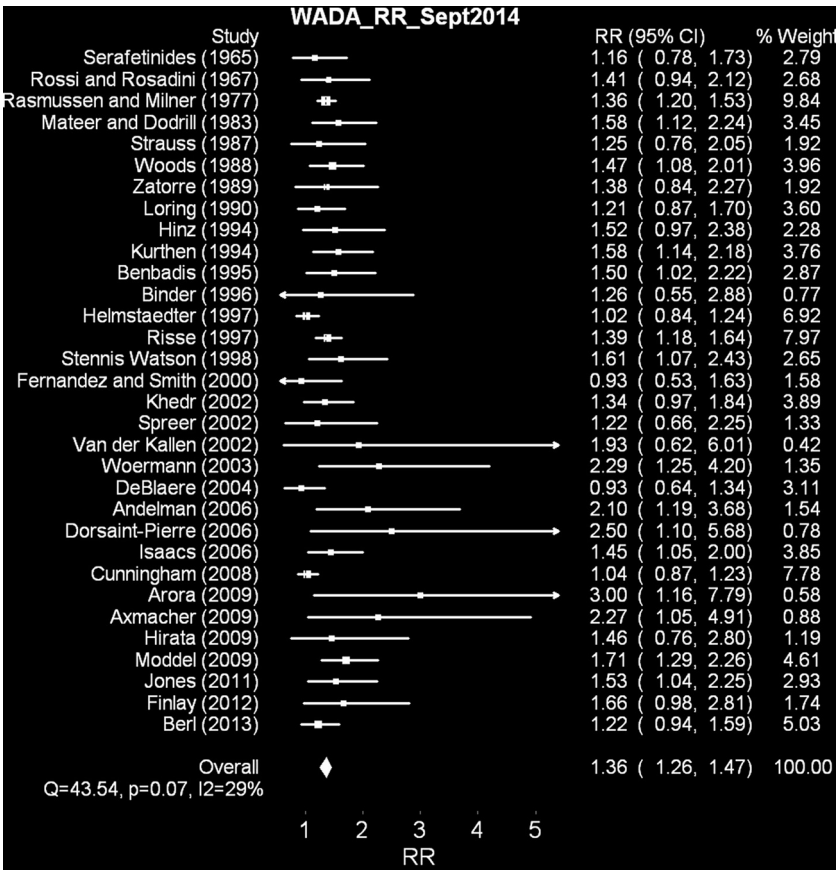


FIGURE 2 | Random effects meta analysis of WADA test left brain dominance relative to anomalous dominance for dextrals relative to adextrals. Note that the range of the 95% confidence intervals for the overall effect, does not overlap zero.

in adextrals, 65%). The former proportion is not radically different from other studies that report WADA data from large dextral samples only (e.g., Benbadis et al., 1995b; see Ocklenburg et al., 2014 for a recent review; also see more rare adextral-only studies such as Perlaki et al., 2013).

DISCUSSION

These results point to increased left hemisphere dominance in dextrals relative to adextrals, in contrast with the left brain damage aphasia incidence data reported in Meta Analysis 1. Of course, there are many scientific caveats related to these samples, most of which are distinct from those related to the aphasia incidence data analyzed above. For example, there is some debate about how to classify individuals as bilateral for speech (surprising, in that a binary speech arrest yes/no classification should be possible after WADA testing; for reviews see Snyder et al., 1990; Baxendale, 2002). For example, Benbadis et al. (1995a) contrast this "arrest, yes or no" kind of approach with duration of speech arrest and relative speech criteria (i.e., L-R/L+R, a type of normalizing laterality quotient much more common in the dichotic listening literature mentioned below). When they adopted 2/3 of these measures to indicate bilateral representation, they could group these patients into bilateral autonomous (either hemisphere on its own can support speech) and bilateral dependent (both hemispheres show equivalent speech arrest). This proportion was roughly 50:50 (but only 19/165 patients achieved classification as bilateral with this set of criteria). They did not find much of a difference between the proportions of dextrals and adextrals in either bilateral or right dominance groups.

The current results suggest more dramatic differences between dextrals and adextrals (in the case of the left hemisphere in particular) than in the aphasia incidence literature summarized in **Figure 1**. One problem for estimating hemispheric asymmetry in non-epileptics from these studies is that, of course, many people suffering from severe epilepsy will have had congenital abnormalities, which may in some instances at least, lead to a change in speech and language dominance from one hemisphere to another. Of course, this caveat *should* apply to the estimates of speech dominance in the dextrals as well as the adextrals (assuming, probably wisely, that epileptogenic foci are rather agnostic about which hemisphere they choose to appear in), unless of course a more complicated "pathological left handedness" argument is made (e.g., Geschwind and Galaburda, 1985a,b,c). Claims for increased incidence of adextrality in epilepsy are extremely common. For example, Kim et al. (2001) claim a 15% incidence of left handedness in a sample of Korean epileptic patients with left

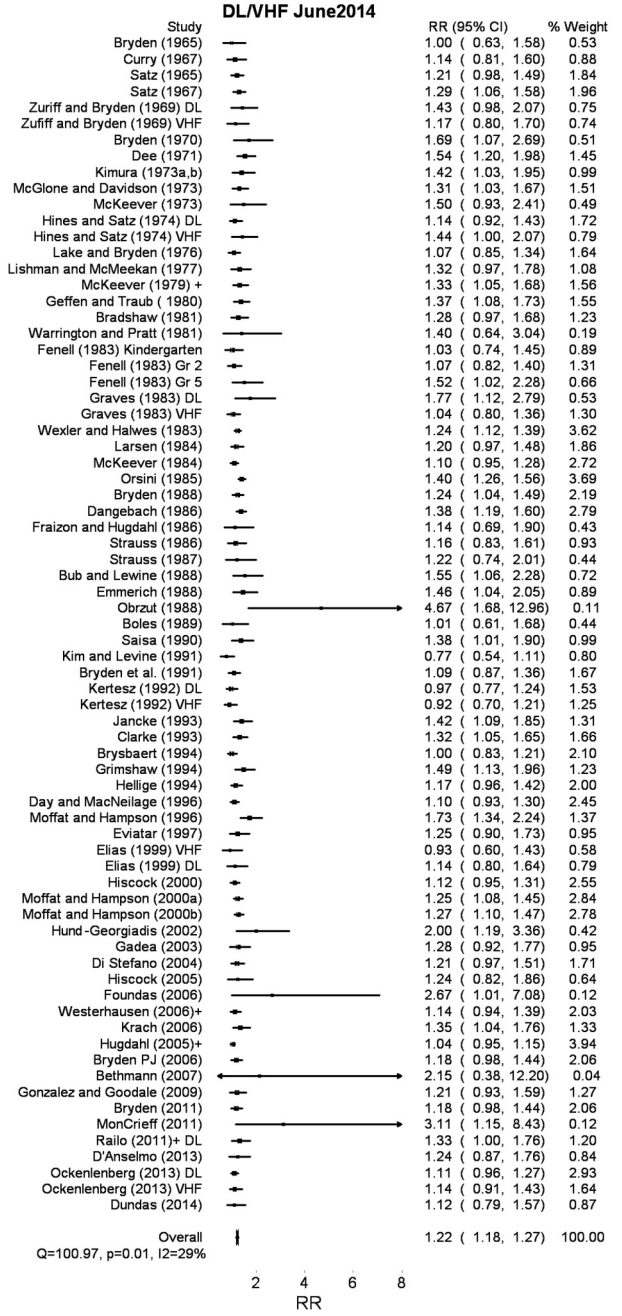


FIGURE 3 | Random effects meta analysis of right ear/right visual field bias for dextrals relative to adextrals.

temporal lobe epilepsy (TLE), compared to a control sample estimate of around 5% (a three-fold increase); strong right handers were more common, but less dramatically so, in a right TLE group (84%) compared to the strong right hander incidence in the control group (67%). However, this sample was selected for medial temporal lobe epilepsy exclusively (and not for testing handedness incidence in epileptic people *per se*), as well as for relatively equal numbers of left TLE and right TLE patients (58 and 51, respectively). In another series, this time of 92 consecutive epileptic people with left hemisphere foci, 71 were right handed (79%), and 20 were left handed or ambidextrous (21%); the comparable numbers with right hemisphere foci were 55 right handers (77%) and 16 adextrals (23%; Stewart et al., 2014). These numbers can be compared to normal incidences in post-World War II Western societies of about 90% dextral, 10% adextal (McManus, 2002). Slezicki et al. (2009) find an increased incidence of adextrality of approximately 6% in American and 3% in Korean samples, totaling 478 people with epilepsy. Dellatolas et al. (1993) do find an increased incidence of left handedness in people with epilepsy, but only significantly so in individuals with brain damage so severe that they were hemiparetic. These data suggest that in some, but not all, series of epileptic patients, adextrality may be slightly more common that is usually detected in non-epileptic samples.

In fact, a little known consideration suggests that the dextrals in the original Montreal Neurological Institute cohort are not a completely random sample of all right-handed epilepsy patients. Reading the fine print of Rasmussen and Milner (1977) reveals that many dextral epileptic patients were *not* routinely given the WADA test prior to their surgeries; for example, those without adextral family members[4]. (Presumably left brain dominance was assumed in these dextral surgical candidates). Of course, if they weren't screened, they could not have contributed to the estimates in **Table 1**. Adextrals, as a matter of course, were tested regularly (also see Rey et al., 1988; Knake et al., 2003, for similar inclusion restrictions in other neurosurgical settings). One would think that the estimates for pre-selected dextrals could be "watered down" with respect to a "true" left hemispheric dominance measure, available only if *all* right handers were routinely administered the WADA. We think that this is unlikely, given near ceiling estimates of left dominance from most WADA studies (which is also consistent with much of the evidence in non-epileptics below), but keep the "pre-selection" issue in mind when reading critiques of WADA as a legitimate estimator of language lateralization in adextrals.

This issue of reorganization after early right or left hemisphere damage has been addressed to some extent by studies such as Stewart et al. (2014), Cunningham et al. (2008), Powell et al. (1987) and others, who identify speech dominance in patients with epileptic foci in the right hemisphere or the left. Eight of these studies are summarized in **Table 2** (sadly, these include four experiments, of many, where only left temporal lobe epileptic patients were included). Samples with small n's (e.g., Staudt et al., 2002), no report of handedness or dextrals only (e.g., Helmstaedter, 1999; Brázdil et al., 2003; Raja Beharelle et al., 2010) or studies which have utilized pre-selection to include more people with anomalous dominance (e.g., Strauss and Wada, 1983) are omitted. Obviously studies that report the number of dextrals and adextrals in the sample, but do not provide separate language dominance for each group as a function of hemispheric locus,

[4]Familial sinistrality was once considered an extremely important moderator of cerebral asymmetries (e.g., Hécaen and Sauguet, 1971; reviewed by Bishop, 1980) but has largely fallen out of favor (e.g., Orsini et al., 1985; Bishop, 1990; although see Willems et al., 2014, which argues for its reinclusion as a moderator variable).

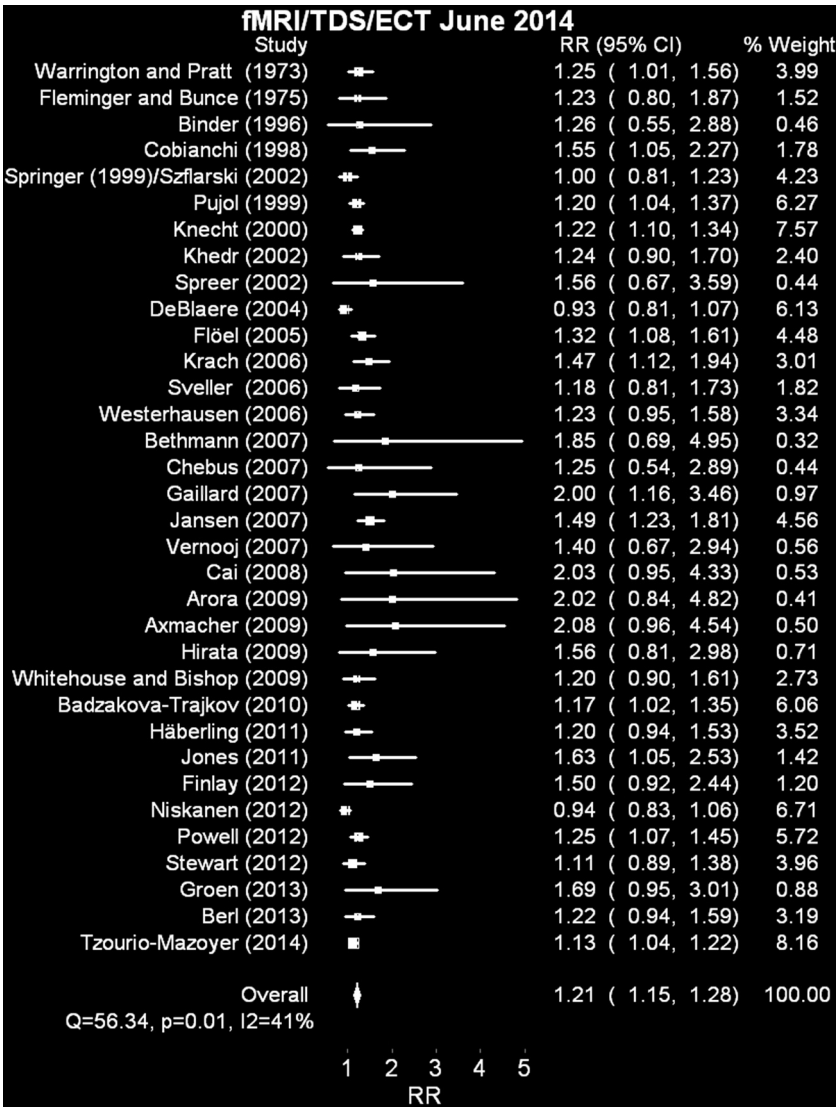


FIGURE 4 | Random effects meta analyses of fMRI + rate ratio of left brain dominance to anomalous dominance in dextrals relative to adextrals. The analysis including the excluded study (Basic et al., 2004) is available as Supplementary Material.

are also not included. A weighted means analysis does support the idea that left lesions (relative to right lesions) do drive up the incidence of anomalous dominance in the adextrals by over 26% (although note the tiny sample sizes) while in dextrals the increase is much smaller (about 11%).

For expediency's sake, another crucial moderator of these effects has been ignored: whether or not the unilateral brain damage occurs early or late in life (the sample sizes in this domain, as usual in the adextrals in particular, do not inspire confidence in the parsimony of quantifying a four-way interaction between handedness group, language dominance, side of focus and age of injury).

In any case, anomalous dominance cannot be completely explained by left hemisphere damage in adextrals. Thirty years of functional and structural neuroimaging alone has put paid to any sort of "all left handedness (and/or anomalous dominance) follows from left hemisphere pathology," pushing a few unfortunate people away from a near 100% right-handed, left-hemisphere dominant phenotype. In fact, we often forget that 5–10% dextrals, by most estimates (see **Table 2**), may have anomalous dominance. Few would argue that these individuals have left hemisphere pathology. The pathological left hander account cannot be dealt with in any detail here. It, in any form, is complicated by the fact that genetic models have yet to account for any causal direction of language dominance-handedness relationships. In other words, any innate plan could be for handedness, which drives, incompletely, speech and language dominance, or, could be for speech and language dominance which drives, incompletely, handedness (see McManus, 1985, 2002; Yeo and Gangstead, 1993; Corballis, 1997; Annett, 2002; Klar, 2003; Armour et al., 2013; for further discussion).

Table 2 | Speech dominance as a function of handedness and side of lesion/epileptic focus.

	Left hemisphere lesions				Right hemisphere lesions			
	Adextrals		Dextrals		Adextrals		Dextrals	
	LD	AD	LD	AD	LD	AD	LD	AD
Cunningham et al., 2008	41% (7)	59% (10)	84% (53)	16% (10)	75% (9)	25% (3)	100% (55)	0% (0)
Gaillard et al., 2007	40% (8)	60% (12)	78% (64)	18% (22)	–	–	–	–
Helmstaedter, 1999	89% (16)	11% (2)	86% (4)	14% (9)	58% (7)	42% (5)	78% (58)	22% (16)
Mbwana et al., 2009	25% (2)	75% (8)	62% (23)	38% (14)	–	–	–	–
Powell et al., 1987	40% (2)	60% (3)	44% (4)	56% (5)	100% (3)	0% (0)	70% (7)	30% (3)
Stewart et al., 2014	55% (11)	45% (9)	85% (60)	15% (11)	94% (15)	6% (1)	93% (51)	7% (4)
Strauss et al., 1990	11% (1)	89% (8)	72% (13)	28% (6)	–	–	–	–
Strauss and Wada, 1983	25% (2)	75% (6)	94% (21)	6% (4)	100% (3)	0% (0)	100% (31)	0% (0)
Sveller et al., 2006	59% (13)	41% (9)	82% (50)	18% (11)	–	–	–	–
Weighted mean	58%	42%	80%	20%	84%	16%	91%	9%

Strauss et al. (1990) do not indicate if any patients overlap with Strauss and Wada (1983) so both are included. Weighted means were calculated as a function of the total number of adextrals or dextrals in the LD and AD columns, separately for left and right hemispheric lesions.

META ANALYSIS 3: INDIRECT TECHNIQUES WITH NEUROLOGICALLY-INTACT PARTICIPANTS

INTRODUCTION

WADA testing of the sort described above became quite a common exercise in neurosurgery clinics from the 1970s onwards; in parallel, experimental psychologists were pursuing less direct methods for examining behavioral asymmetries that are related (in theory) to cerebral asymmetry for language. The two main methods, dichotic listening (where different sounds are presented to the two ears simultaneously) and tachistiscopic studies (visual half fields, presenting stimuli such as words or consonant-vowel-consonant syllables) can provide sensible estimates of cerebral asymmetries that are largely consistent with the aphasia and WADA test research. Unfortunately, the tendency to provide the proportions of any sample of dextral or adextral participants who show, for example right ear or left ear bias, fell out of favor relative to the usual null hypothesis significance tests, contrasting groups defined by handedness (and occasionally, sex, writing posture, familial presence of adextrality, and so on). Inevitably, these rather laborious large n studies began to fall out of favor, partly due to the fact that the results showed that dextrals were more lateralized than adextrals on any particular indirect measure (see Bryden, 1982 for a comprehensive review of the relevant literature from 1960s to the 1980s)[5].

In other studies, particularly ones with smaller sample sizes, mean differences between dextrals and adextrals on any particular dependent measure were not statistically significant, leading authors to conclude that handedness has no effect (e.g., Goodglass and Barton, 1963; Hugdahl et al., 2012) or more recently, that any effects of handedness are small relative to larger effects of more direct measures of language dominance (Van der Haegen et al., 2013b). Remarkably (to us, at least) Kimura herself, who helped launch dichotic listening as a valid paradigm in asymmetry research, had argued from some of her earliest data that dichotic listening scores do not discriminate between dextrals and adextrals (Kimura, 1961). Some years later, Bryden et al. (1983a), argued that hemispheric dominance accounts for about twice as much of the variance in dichotic listening as handedness does.

Nevertheless, these techniques might play some small role in identifying the probable language lateralization of individual people (if, for example, peripheral hearing differences between ears and attentional biases can be ruled out using forced attentional conditions, hearing tests and so on). They may also speak to estimates of the degree of left brain dominance in dextrals and adextrals if several weaker effects can be pooled using the techniques of meta analysis. Therefore, data on proportions of dextrals and adextrals who showed ear or visual field advantages were gleaned from the literature. Kim (1994) has previously performed an early meta analysis on VHF data; however his focus was on variance/central tendency in dextral and adextral groups rather than the proportions of participants in left right or bilateral language dominance categories.

METHODS

To be included in the current meta analysis studies must have provided frequencies of ear advantages (or visual field advantages) in dextrals and adextrals. These are, for historical reasons, more common in dichotic listening studies and much less common in divided visual field experiments (Hugdahl and Franzon, 1985). It may not be surprising to the reader by this point to learn that that many studies (sadly some with remarkably large samples) do not provide these data, and instead rely on inferential statistics on means and variances, test-retest correlations and the like (e.g., Orbach, 1967; Higenbottam, 1973; Briggs and Nebes, 1976; McKeever and VanDeventer, 1977; Hines et al., 1980; Geffen and Caudrey, 1981; Bryden et al., 1983b; Foundas et al., 2006).

[5]A related literature on concurrent hand movements and speech will not be referred to here, as the vast majority of these papers only report measures of central tendency (e.g. Lomas and Kimura, 1976; Sussman, 1982; Murphy and Peters, 1994).

RESULTS

The 73 studies summarized included 6691 dextral and 3497 adextral participants. The results of this random effects meta analysis appear as **Figure 3**. Supplementary Material contains the raw data, and the meta analytic weights associated with each study. It also contains a number of studies not included in the analysis on a separate sheet. The obtained odds ratio of 1.22 (95% CI 1.18–1.27) suggests that dextrals are more likely to show right ear/right visual field advantages relative to adextrals, in spite of considerable heterogeneity again ($Q = 100.97$, $p = 0.01$; $I^2 = 29.69\%$). Of the 73 studies, all but 4 result in rate ratios greater than 1. It may be worth noting that the vast majority of these participants would have been taken from samples of university undergraduates (a population, especially in the selective days of the twentieth century university sector, who would be unlikely to be overly populated by adextrals with subtle left hemisphere pathologies). In Supplementary Material, we have also multiplied each proportion for dextrals and adextrals by the weights assigned by the meta analysis. For dextrals, the weighted mean is 83.2% left hemisphere biased; for adextrals the weighted mean is 68.2%.

DISCUSSION

The direction of these data is consistent with the results of the WADA test analysis above, albeit with a slightly reduced pooled rate ratio in this case (1.22 vs. 1.37). It is difficult to unambiguously interpret this smaller rate ratio (in comparison with the WADA rate ratio reported above) as an effect of reduced sensitivity of indirect tests like DL and VHF experiments. Theoretically, measures that are more indirect would result in higher proportions of participants being assigned to the anomalous dominance category, but we can see no obvious reason why such a bias would interact in some meaningful way with handedness group. The final paradigm-driven meta analysis below may speak to this difference to some extent.

META ANALYSIS 4: FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI), ELECTRO-CONVULSIVE THERAPY (ECT) AND TRANSCRANIAL DOPPLER SONOGRAPHY (TDS)

INTRODUCTION

Other techniques were brought to bear in the 1970s which speak to language lateralization in dextrals and adextrals beyond the indirect perceptual techniques summarized above in Meta Analysis 4. For example, Elizabeth Warrington and Richard Pratt realized that inferences similar to those made using the WADA test could be made by studying speech arrest in patients undergoing electroconvulsive therapy (ECT) for psychiatric disturbances such as depression. In a sample of 55 right handed patients, speech dysfunction was elicited after left skull ECT in 100% of them (Pratt and Warrington, 1972). In a later study, Warrington and Pratt (1973) extended the method to 24 left handers and found left sided speech arrest in 70% of the sample. A later independent study by Geffen et al. (1978) reported 80% left hemispheric dominance in a sample of 31 right handed patients a few years later.

We have grouped ECT, used in this way, with the more modern methods described below as the similarity to transcranial magnetic stimulation (TMS) is a striking one. Of course, by the 1990s, additional technologies have been brought to bear on questions related to language laterality and handedness. Unfortunately (for our purposes here) many of the samples have largely been devoted to documenting the usefulness of fMRI as a replacement for the WADA test (see Medina et al., 2007; Bauer et al., 2014 for reviews of this extensive literature), typically in smaller samples of patients about to undergo epilepsy surgery. We use the term smaller here regarding our purposes of course, which in an ideal world would include many dextrals and adextrals reported on as separate groups. Understandably, these small samples tend to contain very few (if any) adextral participants (Desmond et al., 1995; Binder et al., 1996; Worthington et al., 1997). A similar problem exists for several papers which have attempted to use repetitive TMS for the same purpose (Abou-Khalil, 2007, reviews several of these papers). The exception to this rule is included (Khedr et al., 2002).

Nevertheless, a handful of fMRI—WADA comparison experiments (and a small number of papers using other methods, such as TDS and magnetoencephalography—MEG) have collected either so many participants over time that a number of adextrals are included, or, rarely, have by design pursued additional adextrals (usually to increase likely variance in speech dominance). Thirty-five such studies, as well as large n fMRI studies in non-epileptics which include adextrals, are summarized in **Table 3**[6][7] . Note that many of these experiments will be based on epileptic participants, so will be subject to the same caveats mentioned above regarding WADA study results.

A major concern, well understood by neuroimagers in this field, is the continuous nature of activation data revealed in individuals performing language-relevant tasks in the scanner. For our purposes here, we will ignore methodological differences (particularly those related to decisions regarding defining bilateral speech representation from continuous fMRI data—see Binder et al., 1996; Baciu et al., 2005; Bethmann et al., 2007; Vigneau et al., 2011; for some of the debates regarding precise procedures).

We also include studies in this analysis which use other measurement techniques based on blood flow, such as transcranial Doppler sonography (TDS). The grouping together of such diverse methods (ECT, fMRI, MEG, EEG, and TDS) may alarm researchers who use such techniques regularly. Nevertheless, in our mind they are less comfortably grouped with the aphasia literature, or with the indirect perceptual tasks such as DL or VHF experiments.

It is not surprising that the vast majority of studies examining the cerebral organization of language with these newer paradigms test right handers exclusively (e.g., Neville et al., 1998; Parker et al., 2005; Pillai and Zaca, 2011). On the other hand, some fMRI/EEG/TDS researchers may be biased by the overlap between

[6]Several studies which focussed on dextrals exclusively will not be summarized here. Representative papers that result in cerebral asymmetry classifications largely consistent with the dextral means from fMRI, WADA, ECT and TDS include (Kompus et al., 2012; Ocklenburg et al., 2013).

[7]We are also excluding studies where inclusion criteria influenced the likelihood of increased incidence of anomalous dominance (e.g., Sabbah et al., 2003), with the exception of the pursuit of adextrals of course.

Table 3 | fMRI/ECT/TDS studies of language lateralization.

Study	Dextral n	LD (%)	AD (%)	Adextral n	LD (%)	RD (%)	LD diff (Dex-Adex)
Arora et al., 2009	30	87	13	10	20	75	+67
Axmacher et al., 2009	24	83	17	10	40	60	+43
Badzakova-Trajkov et al., 2010	107	95	5	48	81	19	+14
Benson et al., 1999	11	100	0	8	75	25	+25
Berl et al., 2013	185	75	25	39	62	38	+13
Bethmann et al., 2007	26	92	8	5	50	50	+42
Binder et al., 1996	19	84	16	3	67	33	+17
Cai et al., 2008	10	90	10	9	44	56	+46
Chlebus et al., 2007	12	83	17	3	67	33	+16
Cobianchi and Giaquinto, 1998	18	94	06	18	61	39	+33
Deblaere et al., 2004	14	93	07	4	100	0	-7
Findlay et al., 2012	21	86	14	14	57	43	+29
Fleminger and Bunce, 1975	44	82	18	8	67	33	+15
Flöel et al., 2005	37	97	03	38	74	26	+23
Gaillard et al., 2007	80	80	20	20	40	60	+40
Groen et al., 2013	45	84	16	12	50	50	+34
Häberling et al., 2011	35	91	9	25	76	24	+15
Hirata et al., 2010	54	89	11	7	57	43	+32
Jansen et al., 2007	130	98	02	53	66	34	+22
Jones et al., 2011	47	92	02	16	56	36	+26
Khedr et al., 2002	25	84	16	25	68	32	+16
Knecht et al., 2000	155	95	05	132	78	22	+17
Krach et al., 2006	29	97	03	29	66	34	+31
Loring et al., 1990	91	80	20	12	75	25	+5
Mazoyer (sub)	144	94	06	153	84	16	+10
Niskanen et al., 2012	16	94	06	4	100	0	-6
Powell et al., 2012	42	100	0	40	80	20	+20
Pujol et al., 1999	50	98	02	50	82	18	+16
Spreer et al., 2002	18	78	22	5	40	60	+38
Springer et al., 1999/Szaflarski et al., 2002	50	78	22	50	78	22	0
Stewart et al., 2014	126	88	12	36	72	28	+16
Sveller et al., 2006	61	82	18	13	69	31	+13
Tzourio-Mazoyer et al., 2014	144	94	06	153	84	16	+10
Van der Kallen et al., 1998	14	100	0	6	17	83	+83
Vernooij et al., 2007	10	70	30	10	50	50	+20
Warrington and Pratt, 1973	52	98	02	23	78	22	+20
Westerhausen et al., 2006	42	81	19	47	66	34	+15
Whitehouse and Bishop, 2009	45	80	20	30	67	33	+13
Weighted mean		91%	9%		76%	24%	

Classification techniques vary somewhat, as do criteria for bilateral language classification (hence my grouping of bilateral and right dominance classifications as anomalous dominance). The final column represents the difference between dextrals and adextrals in the percentage of that sample which is left hemisphere dominant. The weights in the associated meta analysis were used to calculated the weighted percentages at the bottom of the table. The difference between the two weighted LD means is equivalent to a risk ratio, dextrals to adextrals, of 1.17.

dextrals and adextrals to the point that handedness is no longer even mentioned in the methods sections of individual papers (e.g., Wang et al., 2012; Bellugi et al., in press). This state of affairs is no doubt exacerbated by the rarity of adextrals in any small or medium sized sample of individuals, patient groups or otherwise.

Other fMRI experiments have contrasted reasonably large samples of dextral and adextral participants on various language, memory and spatial tasks, but the emphasis in analysis is on measures of central tendency from the entire group (e.g., Gur et al., 1982; Cuzzocreo et al., 2009) or they only report main effects or other data that do not allow for the risk ratio calculations used here (e.g., Miller et al., 2005). Structural investigations using techniques such as diffusion tensor imaging (DTI) are now appearing which include dextrals and adextrals as separate groups, but they often do not have functional data on their participants or, as is often the case, focus on measures of central tendency at the group level (Hagmann et al., 2006).

METHODS

Many of the papers included in this analysis were identified by related reference and cited reference searches for classic papers such as Rasmussen and Milner (1977). Literature searches for this set of studies on fMRI and handedness, TDS and handedness, ERP and handedness, included many papers that we then excluded for reasons above. We also identified papers which cite some of the original large n fMRI handedness studies including Benson et al. (1999), Knecht et al. (2000; a large n TDS paper), Pujol et al. (1999), Springer et al. (1999), etc. This final paradigm-based random effects meta analysis uses the data of **Table 3** to create rate ratios for left dominance, dextrals relative to adextrals.

RESULTS

The 35 studies summarized included 1870 dextral and 1066 adextral participants. The results of this analysis appear in **Figure 4**. One unusual TDS paper (Basic et al., 2004) found 92% *right* brain dominance in their adextral group, a highly unusual result (equal to an odds ratio of 11.67 for this particular study, compared to a range of 1.00–2.08 for the other 34 experiments). Therefore, it was dropped from the analysis (Supplementary Material includes it for comparison purposes). The revised overall risk ratio for left hemispheric dominance in dextrals compared to adextrals is 1.21 (95% CI 1.15–1.28; $Q = 56.34$, $p = 0.01$, $I^2 = 41\%$). We also modeled % left dominance in these studies by weighting each group percentage by the meta-analytically derived inverse weighting. This procedure suggests a best estimate, on average, of left brain dominance in dextrals of 90% and in adextrals, 73% (data available on sheet 1 in Supplementary Material).

DISCUSSION

This overall effect estimate is remarkably similar to the one associated with **Figure 3** based on the dichotic listening/visual half field results (overlap between these two meta analyses is less of an issue than overlap between the fMRI/ECT/TDS and WADA test analyses, discussed below in Experiment 6, although three studies do overlap with other paradigm specific meta analyses above).

A META META ANALYSIS?

INTRODUCTION

Recently, advocates of meta analytic techniques have pondered how subgroups can be compared statistically (Schmidt and Hunter, 2015). For example, the rate ratios for the different domains described here can be compared with one another, and the effects on heterogeneity can be modeled by including them all in an omnibus meta analysis. Adding or subtracting different subgroups (in a fashion not unlike hierarchical regression) could reveal informally the relative contributions to heterogeneity. One of the reviewers of a previous version of this manuscript suggested that all of the studies could be included in an omnibus meta analysis, with the degree of heterogeneity across the subgroups established.

According to the Cochrane collaboration (Deeks et al., 2011), such comparisons have to be made with caution. Differences in the magnitude of effects or degree of heterogeneity cannot be unambiguously related to subgroup membership exclusively. For example, in the particular case here, random effects meta analysis will re-weight all of the studies based on the inverse of their variance. This re-weighting means that within experiment sample sizes as well as the number of different experiments identified by the literature search will affect how different studies contribute. Nevertheless, we have performed an overall rate ratio meta analysis using all of the DL/VHF, WADA, and fMRI/ECT/TDS studies.

METHODS

An inverse variance random effects model instantiated in RevMan) 5.0 (2008), provided by the Cochrane Collaboration (http://www.cochrane.org/) was used for the omnibus analysis. It can be downloaded freely here: http://tech.cochrane.org/Revman. The graphical capabilities of this software are rather limited, so we have continued to use MetaXL for the main studies reported above. We used RefMan for this final analysis as it provides decent summary statistics about subgroups in a way that MetaXL does not. Identical rate ratios and confidence intervals are provided by both packages for DL/VHF, WADA tests, and fMRI/ECT/TDS analyses. The Cochrane Handbook recommends random effects for subgroup analysis: "Tests for subgroup differences based on random-effects models may be regarded as preferable to those based on fixed-effect models, due to the high risk of false-positive results when comparing subgroups in a fixed-effect model (Higgins and Thompson, 2004)" (Deeks et al., 2011; 9.6.3.1).

RESULTS

Supplementary Material provides the graphical summary, rate ratios and heterogeneity estimates for the entire analysis as well as the subgroups. Note that the weights applied to each individual study change relative to those computed when each subgroup was subjected to its own meta analysis (**Figures 2–4**). In fact, the sheer number of DL/VHF tests, along with their relatively large numbers of dextral and adextral participants, means that they account for 59.3% of the overall analysis (WADA = 16.5% and fMRI/ECT/TDS = 24.1%). Unsurprisingly, the overall rate ratio estimate is quite similar to those for the DL/VHF and the fMRI/ECT/TDS analyses: 1.25 (95% CI = 1.22, 1.29).

RevMan uses the significance test for subgroup differences recommended by Borenstein et al. (2008). Essentially it tests for heterogeneity across subgroups rather than across individual studies. It also provides an I^2 estimate describing variability due to subgroup differences that is not accounted for by sampling error. We have violated the assumption that the datasets are truly independent, as some participants from WADA tests were also scanned in parallel fMRI/MEG experiments (e.g., Spreer et al., 2002; Axmacher et al., 2009; Hirata et al., 2010). In this instance, the subgroup value of $\text{Chi}^2(2) = 6.69$, $p < 0.05$. $I^2 = 70.1\%$, suggesting significant variability across subgroups. This significant heterogeneity may be largely due to the WADA test subgroup, as an additional "semi" omnibus test including only the 35 fMRI/ECT/TDS experiments and the 72 DL/VHF experiments reveals no significant heterogeneity ($\text{Chi}^2(1) = 0.07$, $p > 0.05$) and a significant rate ratio ($Z = 13.67$, $p < 0.0001$) of 1.22 (95%C.I. = 1.19, 1.26).

DISCUSSION

As noted above, comparing these subgroups has to be done with caution, as there are considerable differences in study number, within study sample size and some non-orthogonality, as some individuals appear in more than one paradigm. Nevertheless, this final analysis does suggest heterogeneity across methods, at least when comparing the WADA test analyses to the others. The analysis supports what the individual meta analyses above suggest—little difference in rate ratios across DL/VHF experiments and the (mainly) more recent studies using fMRI/ECT/TDS methods. There is little overlap of participants between these two sets of experiments. These data are somewhat surprising, given the indirect nature of these behavioral tests and how they may be confounded with attentional and perceptual factors. (Such caveats are rarely made about the results from the newer methods such as fMRI.)

GENERAL DISCUSSION

All of the analyses, bar one, show increased left brain dominance for language in the dextrals of approximately 20%. The least conclusive analysis, in terms of the absolute difference between dextrals and adextrals was for aphasia incidence after left brain damage. Although an effort was made to exclude patient series where some pre-selection was made or implied, it is difficult to evaluate the success of such an enterprise. For example, most of those studies were published pre-1980, which means that, for obvious reasons, additional information about how the experiments were conducted is no longer possible to come by. The most recent, Kimura (1983), for example, parallels her arguments from the 1960s for no difference between dextrals and adextral samples on dichotic listening: she found no differences between her adextrals and dextrals in aphasia incidence after right brain damage (3 vs. 2%, respectively). This sample did show, however, that left brain damage was less likely to lead to aphasia in the adextrals (23% to the dextral 41%). This pattern of data is slightly counterintuitive to our first two meta-analyses, which suggest that aphasia after *right* brain damage separates dextrals and adextrals more effectively.

Is Kimura's sample unusual in some respect? The number of adextrals reported was amongst the better in this kind of study (37 with left brain damage, 30 with right brain damage). She claims that 9% of the sample of patients with unilateral brain damage were adextral (a sensible estimate given what is known about handedness); although her definition of adextrality was quite inclusive (if <7/8 items on her handedness questionnaire indicated the right hand). This kind of in depth analysis of individual papers is dangerous in this context, of course, as scientists tend to be overly analytic of results that are counterintuitive (see below).

The evidence for dysphasia incidence after right brain damage is clearer. The susceptibility of adextrals to dysphasia is over six times higher relative to the dextral samples. In spite of this clear difference, there still remains some uncertainty about whether or not all dextrals and adextrals would have been tested routinely for aphasia after right brain damage. Sadly, these sorts of studies have largely gone out of fashion, in spite of the fact that stroke registers, computerized databases and so forth should mean that these kinds of data could be collated after the fact, in many centers, at a time where much more information about etiology, lesion size and location, could be recorded routinely as part of the electronic record. Handwriting hand, in a pinch, would suffice, if sample sizes were sufficiently large (many handedness researchers may have concerns about such a recommendation). Almost all of the relevant information (in the later twentieth century) related to atypical dominance, lesion location and so on has come from the single case literature on crossed aphasias, apraxias and hemispatial neglect. We argue that the limitations of WADA testing of people with epilepsy are circumvented with the study of patients with acute brain damage.

Aphasia data aside, the other meta analyses differ slightly in terms of the precise rate ratios obtained. The rate ratio from WADA testing (1.36) is somewhat higher than that obtained from the DL/VHF and fMRI/ECT/TDS analyses (1.22 and 1.26, respectively). As **Table 2** shows, language dominance is driven away from the hemisphere of epileptic focus to some extent in both dextral and adextral patients. These issues are discussed in great detail in several analyses (Helmstaedter et al., 1997; Springer et al., 1999; Dijkstra and Ferrier, 2013; Stewart et al., 2014).

In spite of the larger rate ratio obtained from the WADA experiments, the similarity in rate ratios obtained from DL/VHF and fMRI/ECT/TDS is encouraging. Heterogeneity is clearly an issue within both domains ($I^2 = 28.7\%$ for DL/VHF, 62.4% for fMRI/ECT/TDS), but our original suggestion that an inclusive meta analytic approach could cope with some of this heterogeneity is supported by the consistent rate ratios. The convergence from these different domains is noteworthy, given that many neuroimagers are struck by bilateral activations in any language-related task. Cerebral specialization has received less attention in the last 20 years than expected, given its huge importance in the earliest type of "cognitive neuroscience"—neuropsychology.

A rate ratio cannot be used to predict the percentage of dextrals or adextrals who are likely to be left hemisphere dominant for speech. One could use the ratio to predict that value in one group, if the other mean percentage is known or hypothesized. Instead of that kind of calculation, we used the inverse variance weights assigned to each experiment to estimate weighted dominance percentages. The results are interesting, but may need more careful modeling. For DL/VHF, the weighted estimate is 83% left brain dominance in the dextrals; 68% left brain dominance in the adextrals (a 15% difference in the expected direction). For WADA our estimates suggest 87% left dominance in the dextrals and 65% left dominance in the adextrals a 22% difference). Finally, for fMRI/ECT/TDS, the numbers are 88% left dominance in the dextrals and 64% left dominance in the adextrals (a 24% difference). Are there any good theoretical or empirical reasons to place more stock in one of these estimates more than the others?

These estimates, for the dextrals in particular, are slightly lower than the 90%+ predicted by many of the early group studies (e.g., Rasmussen and Milner, 1977). In addition, genetic models such as McManus' DC theory (McManus, 1985) and Annett's Right Shift theory (2000) make similar >90% left dominance predictions for dextrals. Of course any estimates will depend to some extent on how liberal or conservative the criterion is for inclusion in a left brain dominant or no dominance group (grouped with right

brain dominance for our purposes here). For meta analyses and the associated rate ratios, what mattered was that within-study the same criterion was applied to dextral and adextral groups. These estimates for left brain dominance would change with criteria: for example in the work of Brysbaert, Van Der Hagen and their colleagues, a conservative criterion was adopted to ensure strong hemispheric asymmetry in a number of identified individuals. That criteria results in estimates of no atypical dominance in dextrals and about 10% in adextrals (Brysbaert et al., 2012; Van der Haegen et al., 2013a,b) well below the estimates derived in the present analysis. It may be that our estimates of left brain dominance of 85% in dextrals may be somewhat conservative, by assigning more weak "left hemispheric" scores on tasks such as dichotic listening to a no dominance grouping.

Each of these research domains has its own associated weaknesses and strengths for helping to determine the underlying distributions of cerebral asymmetry. WADA testing, as noted above and elsewhere, is limited methodologically for several reasons (what counts as speech arrest, test-retest reliability, etc.), but the most concerning limitation is that congenital brain damage may bias dominance in some unknown (and unknowable) proportion of the patients (see **Table 2**). A strength of WADA, however, is the relatively unambiguous trichotomous data that it provides.

These estimates are in stark contrast to those from neuroimaging, where several methodological issues make simple left, right, bilateral classifications more contentious. For example, calculating a laterality index from functional data requires some hard decisions about regions of interest and thresholding (e.g., Jansen et al., 2006; Abbott et al., 2010), equating regions from each hemisphere which are not structurally identical (Shapleske et al., 1999), and the nature of baseline conditions (Seghier, 2008). Practical issues for imaging include expense (these asymmetry studies benefit from large sample sizes) and the difficulties inherent with interpreting data from single participants (Bosch, 2000; Fedorenko et al., 2010).

Sample size and expense are not particularly crucial issues for DL/VHF studies with neurotypical university undergraduates. These methods, as discussed above, are the most indirect measures of brain asymmetry, have relatively poor test-retest reliabilities and estimates in single participants can be seriously distorted/biased by attentional strategies, task demand and the like.

A reviewer of a previous draft suggested rating studies for their quality (i.e., presence of absence of the different cofounding effects mentioned above, for example) in order to evaluate the sources of heterogeneity more carefully. This suggestion is indeed tempting, as several of the estimates in each domain strike us as improbable, but were included nevertheless (with one exception in the fMRI/ECT/TDS paradigm analysis). In fact, after generating each forest plot it is extremely tempting to discard the wilder appearing estimates which appear outside the range of the other studies. In the ideal world of "new statistics," file drawer problems and biases against null effects and the like would be minimal, as ideally all datasets would be available electronically for meta analytic use (Cumming, 2012, 2013). We do not as of yet operate in such a world. Impressions about quality inevitably will reflect some of the personal biases about what the "true" differences between dextral and adextrals are. Another difficulty with a quality approach is that for many of the possible sources of noise discussed above and in detail elsewhere, their presence, absence or magnitude is hard to quantify. In some cases (as suggested by Kimura, 1983 regarding the aphasia incidence literature), there are reasons to suspect whether or not samples are truly random, or that all dextrals and adextrals were tested and none were preselected in any fashion whatsoever. In a few instances, the samples were not selected for writing hand alone. We have largely ignored historical covariates like familial sinistrality, foot preference or sex, as these tended to apply to both dextral and adextral samples in a similar fashion (in so far as we could tell). Nevertheless, it's likely they would muddy the waters somewhat, if the focus was restricted to a small number of key experiments.

THEORETICAL SIGNIFICANCE OF PROPORTIONS OF DEXTRAL AND ADEXTRAL LANGUAGE DOMINANCE

Excessive concern over precise estimates of cerebral dominance in adextrals, relative to dextrals, might seem a rather specialist sort of worry. Obviously, if the proportion of left hemisphere dominance in adextrals is much higher than these meta analyses suggest, then adextrals and dextrals may not differ in this aspect. Such a result would remove at least one of the major sources of neuropsychological interest in handedness. On the other hand, if adextrals (or very strong left handers at least; see Knecht et al., 2000) were largely right hemisphere dominant for speech, the so-called "Broca's rule" would actually apply, therefore much of the mystery surrounding left handers would largely disappear (i.e., handedness and cerebral dominance for speech and language would predict one another in some direct fashion). The present data, in spite of some of the limitations discussed above, suggest a more complex relationship between handedness and cerebral specialization than either of those two extremes. Practically speaking, a more precise estimate of the degree of language dominance, in both dextrals and adextrals, does have important ramifications, in at least three ways.

First, identifying the more appropriate "phenotype" for many studies (behavioral, genetic, neuroimaging, EEG etc.) could be aided considerably by knowing how many (and which) adextrals have crossed or uncrossed control of speech and limb function. For example, studies of asymmetries that tend to favor the right hemisphere in dextrals, such as face processing (Kanwisher, 1997; Yovel et al., 2008; Meng et al., 2012) and in particular, functions related to paralinguistic aspects of speech such as prosody (van Rijn et al., 2005; Ross and Monnot, 2008) would benefit greatly from knowing which individuals are largely left or right hemisphere dominant for typical speech and language function. In fact, an older literature on "complementary hemispheric specialization" (Bryden et al., 1983a; Elias et al., 1999a,b) has been largely forgotten about, but is ripe for a revival (Cai et al., 2013).

Similarly, organization of subregions of left hemisphere networks in individual or groups of dextrals (Fedorenko et al., 2012a,b) could be contrasted with their counterparts in right dominant individuals, if they could be identified at the individual or small group level. Additionally studies of increased incidence of adextrality in conditions such as dyslexia, autism, developmental coordination disorder and language-specific impairment might

be more conclusive if cerebral control of hand and speech were the independent variables, rather than handedness (typically restricted to writing hand).

Second, more precise estimates of language dominance proportions could open up new studies of manual behaviors, particularly ones which are *not* hand-writing. It may be that one of more of these other manual behaviors (e.g., reaching and grasping, for example; Gonzalez et al., 2007; Gonzalez and Goodale, 2009) or gesturing (Kimura, 1973a,b) might be right hand biased in a significant proportion of "left" handers (as defined by writing hand). In other words an ideal predictor of cerebral dominance for language would be right hand biased in approximately 85% of a sample of dextrals, and 65% of a sample of adextrals. Sadly, almost all studies which contrast dextrals and adextrals on measures of hand choice, hand preference patterns, indirect measures of asymmetry such as DL and VHF studies, and so on inevitably report measures of group tendency and variability and fail to say anything about subgroups (of particular relevance in the adextral samples if sufficiently large and well characterized). Our suspicion is that these possible predictor behaviors need to be measured in the lab or the real world, rather than reported on via a paper and pencil questionnaire (Carey et al., 2009; Gonzalez and Goodale, 2009).

For example, the relatively poor correlations between VHF and DL experiments, or test-rest correlations with the same measures might benefit from a more considered analysis of proportions of the samples who show effects in one direction or the other. A test might have poor reliability because its precise estimate is noisy, yet it might classify individuals dichotomously quite well. It seems probable that people with larger scores on these indirect tests might be less likely to show significant changes on retest (at least in direction), in which case participant performance could be examined more carefully in the individuals who score nearer to zero (are they following task instructions, are they in fact less lateralized across many measures etc.). This kind of approach presupposes a more considered analysis of an individual's performance on two versions of the same test or across different indirect tests.

A third reason why precise estimates of language dominance are of interest is related to sensorimotor control and handedness. In the vast majority of dextrals, the hemisphere more specialized for speech and language is largely in control of the dominant hand, at least at the levels of motor/premotor output and somatosensory input. From a handedness perspective, clearly something very different is going on in the majority of adextrals. In this context, (related to, but not synonymous with, motor theories of speech perception; e.g., Lieberman, 2006; MacNeilage, 2008), there should be subtle benefits ("privileged access") in sensorimotor control for having the dominant hand intimately interconnected with the motor, premotor and somatosensory cortices of the same hemisphere that largely controls the speech musculature (Goodale, 1988; Carey and Otto-de Haart, 2001). A corollary of this idea is that, for the *majority* of adextrals, the non-dominant hand might enjoy benefits for the same reason, at least when compared to the non-dominant hand of dextrals, which statistically, is likely to have privileged access to attentional and visuospatial networks (Mieschke et al., 2001; Carey and Liddle, 2013). Surprisingly, very few studies compare absolute levels of performance in these "four hands" (the few that do are typically a little underpowered when it comes to the size of the adextral sample; e.g., Goodale, 1990; Boulinguez et al., 2001).

In conclusion, efforts to establish precise estimates for dextral and adextral language asymmetry are challenged by pre-selection biases, poor sample sizes, and incomplete reporting of data. The tendency for adextrals to be left hemisphere dominant is conceived (by different scientists) to be an unwanted source of heterogeneity (they therefore just test dextrals). Another approach is to ignore adextrals altogether (e.g., don't record handedness at all, or at least don't report it), as they are relatively rare folk who, for the most part, are arranged as the right handed majority anyway. Nevertheless, these meta analyses reinforce the idea that adextrals have an unusual cerebral arrangement vis-à-vis the control of speech and language vs. control of their dominant hand.

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SUPPLEMENTARY MATERIAL

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Effect of handedness on the occurrence of semantic N400 priming effect in 18- and 24-month-old children

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It is frequently stated that right-handedness reflects hemispheric dominance for language. Indeed, most right-handers process phonological aspects of language with the left hemisphere (and other aspects with the right hemisphere). However, given the overwhelming majority of right-handers and of individuals showing left-hemisphere language dominance, there is a high probability to be right-handed and at the same time process phonology within the left hemisphere even if there was no causal link between both. One way to understand the link between handedness and language lateralization is to observe how they co-develop. In this study, we investigated to what extent handedness is related to the occurrence of a right-hemisphere lateralized N400 event related potential in a semantic priming task in children. The N400 component in a semantic priming task is more negative for unrelated than for related word pairs. We have shown earlier that N400 effect occurred in 24-month-olds over the right parietal-occipital recording sites, whereas no significant effect was obtained over the left hemisphere sites. In 18-month-olds, this effect was observed only in those children with higher word production ability. Since handedness has also been associated with the vocabulary size at these ages, we investigated the relationship between the N400 and handedness in 18- and 24-months as a function of their vocabulary. The results showed that right-handers had significantly higher vocabulary size and more pronounced N400 effect over the right hemisphere than non-lateralized children, but only in the 18-month-old group. We propose that the emergences of right-handedness and right-distributed N400 effect are not causally related, but that both developmental processes reflect a general tendency to recruit the hemispheres in a lateralized manner. The lack of this relationship at 24 months further suggests that there is no direct causal relation between handedness and language lateralization.

Keywords: semantic priming, ERPs, N400, handedness, vocabulary, children

INTRODUCTION

It is frequently stated that right-handedness reflects hemispheric dominance for language (for instance, left hemisphere for phonological processing and right hemisphere for prosody). One explanation often given is that the main language functions are processed by the left hemisphere and that the left-hemisphere is specialized for processing fast temporal transitions, which are involved both in language and in precision skills (for review, see Minagawa-Kawai et al., 2011). Yet, the basis on which it is argued that language lateralization and handedness are related is that most right-handers also process the phonological aspects of language with their left hemisphere, in typical (Knecht et al., 2000) and atypical (Frey, 2008) populations. However, even if two factors completely independent were driving 90% of the population toward right-hand preference for one, and 92% of the population toward processing phonological aspects of language in the left hemisphere for the other one, statistical calculations show that chances that an individual is right-handed and processes language with the left hemisphere would be as high as 83%. Thus, other arguments than correlations are needed to decide whether right-handedness and brain asymmetries in language processing have any cross causality or share a common causality. One argument could be that handedness and hemispheric specialization for language develop in close relation to each other, for instance that one influences the development of the other. In adults, the N400 effect in semantic priming tasks is often distributed over the right hemisphere (Bentin et al., 1985; Kutas et al., 1988; Van Petten and Luka, 2006) and as a first step toward evaluating the relation between handedness and language lateralization during development, we investigated toddlers' handedness and right-hemisphere N400 semantic priming effect during language processing.

THE DEVELOPMENT OF LANGUAGE, OF LANGUAGE LATERALIZATION, AND OF HANDEDNESS

Both handedness and language lateralization have their source very early in life. Concerning handedness, a predominant use of the right hand in most fetuses has been observed as early as 15 weeks of gestational age (Hepper et al., 1991), and this is related with hand preference 12 years later (Hepper et al., 2005). When reaching becomes clearly cortically controlled, after 4–5 months of age, infants show hand preference (Michel et al., 2006), in particular when grasping requires precision (Fagard and Lockman,

2005). Infants show hand preference as soon as they start mastering a new complex skill, such as bimanual complementary actions (Potier et al., 2013) or tool use (Rat-Fischer et al., 2013). In addition, hand preference for reaching only slightly and non-significantly increases from 6 to 7 months to the second year of life (Jacquet et al., 2012). Thus, by 18 months of age handedness is rather well established, at least for the majority of infants.

As regards language lateralization for perception, very early signs have been observed. At birth, some studies using habituation (Bertoncini et al., 1989) or auditory reinforcement (DeCasper and Prescott, 2009) in non-nutritive sucking showed a right ear advantage for processing changes in syllables but this has not been always confirmed in other behavioral studies (Vargha-Khadem and Corballis, 1979; Best et al., 1982). However, a recent functional Magnetic Resonance Imaging (fMRI) study has shown more activation of the left hemisphere in processing changes in syllables in 29-week premature infants (Mahmoudzadeh et al., 2013; see also Kasprian et al., 2011). In addition, other brain imaging studies confirmed left-hemisphere greater activation for phonological processing at or around birth (Pena et al., 2003; Gervain et al., 2008). This early lateralization is compatible with earlier data on structural asymmetry of the language areas of the brain observed in post-mortem fetal (Chi et al., 1977) and *in vivo* brain imaging infant studies (Dubois et al., 2009). Concerning the functions typically involving the right hemisphere in adults, such as processing of pitch contour and prosody, it appears to be processed by the right hemisphere already at 3 months of age (Homae et al., 2006; Grossmann et al., 2010).

Lateralization of language production has also received interest: for instance, Trevarthen noted that the first cooings are often accompanied by movements of the right hand (Trevarthen, 1996). Mouth opening during babbling, but not during smiling, is asymmetrical to the right side (Holowka and Petitto, 2002). Communicative pointing, more often right-handed than object grasping (Cochet and Vauclair, 2010; Cochet et al., 2011; Esseily et al., 2011), is lateralized almost from its start (Blake et al., 1994; Vauclair and Imbault, 2009; Jacquet et al., 2012). Finally, symbolic gestures are more often performed with the right hand than non-symbolic gestures (Bates and Dick, 2002).

There are a few studies on the relation between language development itself and handedness. For instance, according to Ramsay (1984) infants begin to demonstrate unimanual right-handedness on the week of babbling onset, whereas they don't show any significant hand preference on the preceding week(s). A more recent longitudinal study has shown that when hand preference is evaluated between 6 and 14 months, the group of infants clearly categorized as right-handed was significantly more advanced in language evaluated by Bayley scales at 24 months than the group of infants categorized as having uncertain hand preference (Michel et al., 2013). It was also found that the amount of communicative pointing, a recognized prelinguistic skill (Bates et al., 1975), was related to handedness (Cochet et al., 2011; Esseily et al., 2011).

In contrast, the studies on the relation between the development of language lateralization and handedness are scarce and the few existing studies are not in favor of a strong relationship between both asymmetries during early development. For instance, in the communicative pointing longitudinal studies left-handers for grasping were often observed to be right-handed for pointing, and no correlation between developmental change in handedness for pointing and for grasping was observed (Vauclair and Imbault, 2009; Cochet and Vauclair, 2010; Jacquet et al., 2012). However, comparing hand use for communicative pointing with hand use for grasping objects is an indirect way to establish a relation between language lateralization and handedness. To our knowledge, no studies tackled the question of the relationship between the development of language lateralization and the emergence of handedness. In the study presented here we observed the relationship between handedness and the right-lateralized N400 event-related potential (ERP) in a semantic priming task.

Semantic priming provides a tool to study the organization of words in lexical-semantic memory (e.g., Meyer and Schvaneveldt, 1971; Kutas and Hillyard, 1989; Lucas, 2000). In ERP studies in adults, a negative waveform that peaks between 350 and 550 ms post-stimulus onset is more negative for unrelated than for related prime-target word pairs (e.g., Bentin et al., 1985; Holcomb, 1988; Brown et al., 2000). This is called the N400 effect. The N400 effect is typically strongest over the central and parietal recording sites, and it is stronger over the right hemisphere recording sites in adults, especially for written words (e.g., Bentin et al., 1985; Kutas et al., 1988; Van Petten and Luka, 2006), but more symmetrically distributed for auditorily presented words (for review, see Van Petten and Luka, 2006).

In our recent study, we recorded the ERPs during an auditory semantic priming task in young children in order to ascertain whether words in long-term semantic memory storage are organized by their semantic relatedness in 18- and 24-month-olds (Rämä et al., 2013). The results showed that the N400-like priming effect occurred in 24-month-olds over the **right** parietal-occipital recording sites. In 18-month-olds, the effect over the right parietal-occipital recording sites was observed similarly to 24-month-olds only in those children with higher word production ability. This is in accordance with previous studies showing that the right-lateralized N400 response is dependent on productive skills (Friedrich and Friederici, 2004, 2010; Torkildsen et al., 2006) suggesting right-hemispheric distribution might reflect maturity in lexical-semantic processing. Typically, the second year of life is associated with a significant increase in word comprehension and production (Bloom, 1973; Reznick and Goldfield, 1992; Meints et al., 1999; Ganger and Brent, 2004). This vocabulary burst is suggested to be related to advancing in word segmentation, development of naming insight, and ability to categorize objects (for review, see Ganger and Brent, 2004).

The influence of handedness on the magnitude of N400 has never been reported in children. Since right-handedness has been associated with advanced language processing in early childhood, as seen previously, we hypothesized that not only vocabulary size but also handedness would be related to the occurrence of the N400 effect. In our previous study (Rämä et al., 2013), we did not report the results of handedness evaluation but handedness was evaluated in most of the children who participated to the study. In the current study, we included only those children whose

handedness, vocabulary, and N400 effect was measured, and we reanalyzed our data.

METHODS

SUBJECTS

Sixteen (5 girls and 11 boys) 18-month-old (range: 17 months 21 days to 19 months 2 days) and sixteen (11 girls and 5 boys) 24-month-old (range: 23 months 24 days to 25 months 24 days) children from monolingual French-speaking families were included in the current study. The parents gave informed consent before participation. The comprehensive and productive vocabulary size was tested by a French translation and adaptation of the MacArthur Communicative Development Inventory for Words and Sentences (CDI; Fenson et al., 1993). Parents filled the CDI at home, within a week or two after the experiment. Eleven additional children were rejected from original study (Rämä et al., 2013) since they did not pass the handedness test and/or parents did not provide the CDI. All children were born full-term and none of them suffered from hearing or language impairment.

HANDEDNESS EVALUATION

We used the baby handedness test (BbHtest, Sacco et al., 2006). The BbHtest comprises five items to test simple grasping and two items to test precision grasping. Objects for testing *simple grasping* were small baby toys: three Playmobil® figurines, one hand-shake toy (maracas) and a teether. For *precision grasping*, one task consisted in taking a very thin red tube (6 mm in diameter) inserted in a slightly shorter transparent tube from which only the top protruded and the other task consisted in grasping a small horse inserted in a container that was 30 mm in height. To favor unimanual grasping, these two objects were presented so that the infants could not grasp the container, but only the object inside. The baby laterality test thus comprised seven items in total. All objects were presented within reaching distance of the infant at a midline position.

WORD STIMULI

The stimuli were one-, two-, or three-syllable French basic level nouns from seven different categories (animals, clothes, body parts, food, furniture, transportation, and household items). The word categories were chosen from the CDI. The stimuli were arranged into 72 prime-target word pairs (see, for details Rämä et al., 2013). There were 36 words for each trial type (unrelated primes, related primes, and target words). Half of the word pairs consisted of categorically (but not associatively) related words (e.g., train-bike) and half of them of categorically unrelated words (e.g., chicken-bike). Each target word was presented twice; once in the related and once in the unrelated condition. The same word pairs were presented twice during the experiment. The words were recorded and edited with Cool Edit 2000 (Syntrillium Software Corp., Phoenix, AZ) and Pratt (version 5.3.02) programs. The sound levels were normalized among the speakers and words. The speakers were four native French female speakers and they were asked to pronounce the words slowly. Prime and target words in a given trial were always spoken by a different speaker not to allow children to rely on acoustic features. In addition, it had been shown that the speaker variability facilitates word learning in children (Richtsmeier et al., 2009).

EXPERIMENTAL PROCEDURE

During the EEG recordings, children were seated on their caregiver's lap or by themselves in a dimly lit room facing loudspeakers and a computer screen at the distance of 100–120 cm. Parents were informed of the purpose of the study before signing the consent. They were instructed not to communicate verbally or non-verbally with their child during the actual experiment. To keep the children distracted during the experiment, they were allowed to play with small toys positioned on the table in front of them during the experiment. Also colorful pictures from children's books were presented on the computer screen during the experiment but they were not synchronized with auditory stimulation. Children were allowed to choose to look at the pictures or play with the toys. There was no relatedness between words and pictures. A new picture appeared every 15 s.

The interstimulus interval (ISI) was 200 ms between the prime and the target words in each word pair and the intertrial interval (ITI) between the word pairs was 2200 ms. Stimulus onset asynchrony (SOA) varied between 635 ms and 1266 ms (mean SOA = 910 ms, SD = 166 ms). The experiment was divided into four blocks, and there were short breaks between the blocks. Words from different semantic categories were randomly distributed across the blocks. Each word pair was repeated twice during the experiment, but never within the same block. The handedness evaluation was performed either before or after the EEG experiment. The whole experiment lasted 10 min. The study was approved by the Ethical Committee of the University of Paris Descartes, and the experimental procedure was conducted in accordance with the principles of the Declaration of Helsinki (1964).

EEG RECORDINGS

Continuous electroencephalogram (EEG) was recorded (bandpass = 0.1–100 Hz, sampling rate = 250 Hz) from 62 electrodes using a Geodesic Sensor Net (GSN, NetStation EGIS V2.0, with 10–10 international electrode system) referenced to the vertex during the acquisition. Impedances were kept below 50 kΩ. EEG was filtered (0.3–30 Hz), segmented (1200 ms, beginning 200 ms before target word onset to 1000 ms post-stimulus), and ocular artefacts were removed with an ocular artefact removal (OAR) algorithm (Gratton et al., 1983). The 200-ms pre-stimulus period determined the baseline for amplitude measures. The epochs including artefacts (eye-movements, blinks, motion artefacts exceeding ± 150 μV in any channel) were automatically excluded. Epochs including more than 20 contaminated channels were rejected as well. Channels marked as bad were replaced with other channels in proximity using spherical spline interpolation. The epochs were averaged separately for each subject and type of target (related and unrelated) word. The averaged waveforms were re-referenced to the average reference and baseline corrected. The epochs were grand-averaged across all participants in each age group for the type of target word. In the original study, participants with less than 10 trials *per* target word type were rejected. The mean number of trials after the artefact rejection was 26

(13–42 trials) and 22 (11–51 trials) for related and 25 (13–39 trials) and 20 (10–50 trials) for unrelated target words in 18- and 24-month-olds, respectively.

DATA ANALYSES

Handedness

To assess handedness on the BbHtest, a laterality index (LI) was calculated using a classical formula [RH grasps − LH grasps/(RH grasps + Lh grasps + bimanual grasps)] (Michel et al., 2002; Fagard and Lemoine, 2006). From the LI, the children were characterized as right-handers (LI $\geq$ 0.5), left-handers (LI ≤ -0.5), or non-lateralized (LI comprised between −0.51 and 0.49).

Vocabulary

The participants in each age group were divided into two vocabulary groups based on their productive vocabulary scores obtained in McArthur Communicative Development Inventory for Words and Sentences. The mean vocabulary score was calculated for each participant and the median score of all participants was used to divide them into two groups, named low and high producer groups. The mean number of words produced by 18-month-olds was 43 ($SD = 54$, median = 24.5). Here we decided to eliminate, for the analyses as a function of the vocabulary, two 18-month-old children whose number of words was too close to the median (24 and 25 words). The mean number of words produced by 24-month-olds was 241 ($SD = 154$, median = 269.5). We also eliminated, for the analyses as a function of vocabulary group, one 24-month-old child whose number of words was close to the median (261 words), and lower than the median but higher than the mean.

ERPs

In the original study (Rämä et al., 2013), a significant N400 effect was obtained over the right posterior-parietal recording sites. The magnitude of N400 component in response to related and unrelated target words was measured by calculating the mean amplitude of the component within 200-ms-windows. To analyze the significance of the component, a repeated measure of analysis of variance (ANOVA) included as within subject factors: trial type (related vs. unrelated), area (frontal, central, and parietal-occipital), hemisphere (left vs. right), and time interval (five 200-ms time windows starting from 0 to 1000 ms), and as a between subject factor the vocabulary (high producers vs. low producers). The data were analyzed using the SPSS statistical package (IBM SPSS statistics, version 20) and all ANOVA results were Greenhouse-Geisser corrected. According to the 10–10 international electrode position system, the sensor positions of the right parietal-occipital area were the following: P2, P6, P8, P10, PO4, PO8, O2, and TP10. The N400 effect was more pronounced for unrelated than for related targets during the first, second, and the third time intervals over the right hemisphere [$t_{(22)} = 2.34$–3.23, $p < 0.05$–0.005]. Here, we report the results of the effect of handedness and vocabulary on the magnitude of this previously found significant right-lateralized N400 effect.

Statistical analyses

Chi-square tests were used to analyze the distribution of right-handed vs. non-lateralized children as a function of vocabulary. We used ANOVA to test the effect of age, level of vocabulary and handedness on the N400. Finally, we calculated correlations between the raw values of LI, number of words and N400.

RESULTS

VOCABULARY

At 18 months, in the low producer group, the average score was 8 words ($SD = 4.5$; range: 0–15 words) and in the high producer group the average score was 83.3 words ($SD = 62.7$; range: 29–214 words). At 24 months, in the low producer group, the average score was 102 words ($SD = 91.3$; range: 4–243 words) while the average score in the high producer group was 360 words ($SD = 90.1$; range: 278–555 words).

HANDEDNESS

The LI increased slightly but not significantly ($p = 0.20$) between 18- ($m = 0.36$, $SD = 0.5$) and 24-month-olds ($m = 0.58$, $SD = 0.5$). There were more right-handed than non-lateralized children and only one left-hander in each age group (see **Table 1**). A chi-square on the distribution of handedness as a function of age showed also no significant age effect ($p = 0.84$).

RELATIONSHIPS BETWEEN VOCABULARY, N400 EFFECT, AND HANDEDNESS

Vocabulary and handedness

Since there were only two left-handers, we did not include them in any statistical analysis, but they are briefly mentioned and their values are indicated on the graphs.

At 18 months, the proportion of children with a high vocabulary score was greater among right-handers (71.4%) than among

Table 1 | Distribution of handedness category based on the laterality index in 18- and 24-month-olds.

	18-months	24-months	All subjects
Right-handers	9 (56.2%)	11 (68.7%)	20 (62.5%)
Non-lateralized	6 (37.2%)	4 (25%)	10 (31.2%)
Left-handers	1 (6.2%)	1 (6.2%)	2 (6.2%)
Total	16	16	32

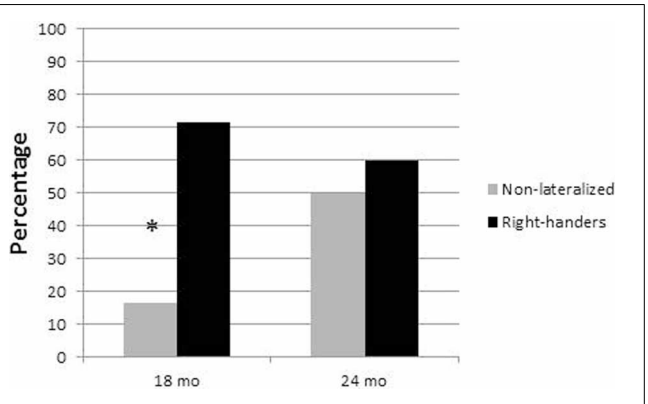


FIGURE 1 | Percentage of children with high vocabulary as a function of age and handedness. *$p < 0.05$.

non-lateralized (16.7%, see **Figure 1**). A chi-square on the distribution of handedness as a function of vocabulary at 18 months showed a significant effect [$\chi^2_{(1)} = 3.9, p < 0.05$]. At 24-months, the proportion of children with a high vocabulary score was only slightly greater among right-handers (60%) than among non-lateralized (50%), and a chi-square on the distribution of handedness as a function of vocabulary at 24 months showed no significant effect ($p = 0.73$). The correlations between number of words and LI were 0.38 at 18 months and 0.06 at 24 months.

N400 effect and handedness

At 18 months, only the right-handers had a right-distributed N400 effect whereas 24-month-olds from all handedness categories had the N400 effect (see **Figures 2**, **3**). An ANOVA of the N400 as a function of age and category of handedness (non-lateralized vs. right-handed) showed no significant main effects of age ($p = 0.18$) or category of handedness ($p = 0.63$), but the interaction between age and category of handedness was significant [$F_{(1, 26)} = 6.3$, $p < 0.02$]. A Fisher LSD *post-hoc* test indicated that the N400 effect obtained in non-lateralized children differed significantly from that in right-handed children at the age of 18-months ($p < 0.05$), but not at 24 months ($p = 0.18$). The correlations between N400 and LI were -0.52 at 18 months ($p < 0.05$) and 0.29 at 24 months.

N400 effect, vocabulary, and handedness

Finally, we looked at the N400 as a function of age, handedness and vocabulary. As can be seen in **Table 2**, at 18 months the right-handers with high vocabulary had the most negative N400 effect and the non-lateralized children with low vocabulary was the only group without N400. At 24 months, the non-lateralized children with a high vocabulary had the most negative N400. Children with high vocabulary (right-handed and non-lateralized) had a slightly larger N400 than children with low vocabulary. An ANOVA was calculated on the N400 effect with age (x 2), handedness (x 2, Right-handed vs. Non-Lateralized) and vocabulary (x 2, High vs. Low) as independent variables. It showed no main effect of age ($p = 0.57$), no main effect of handedness ($p = 0.97$) but a main effect of vocabulary [$F_{(1, 19)} = 5.7, p < 0.05$]. None of the interactions were significant. A *post-hoc* LSD test showed that, within the same age groups, the 18-month-old right-handers with high vocabulary and the 18-month-old non-lateralized children with low vocabulary differed significantly ($p < 0.01$); similarly, the 24-month-old non-lateralized children with high vocabulary differed significantly from the right-handers with low vocabulary ($p < 0.05$).

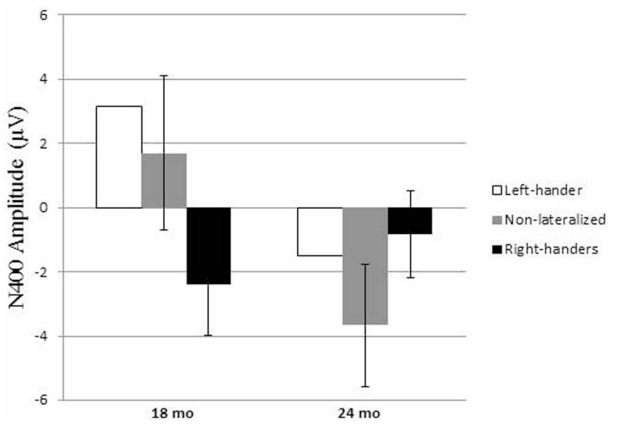


FIGURE 3 | The N400 effect size as a function of age and handedness (The two left-handers are represented here even though, for obvious reason, they were not included in the ANOVA).

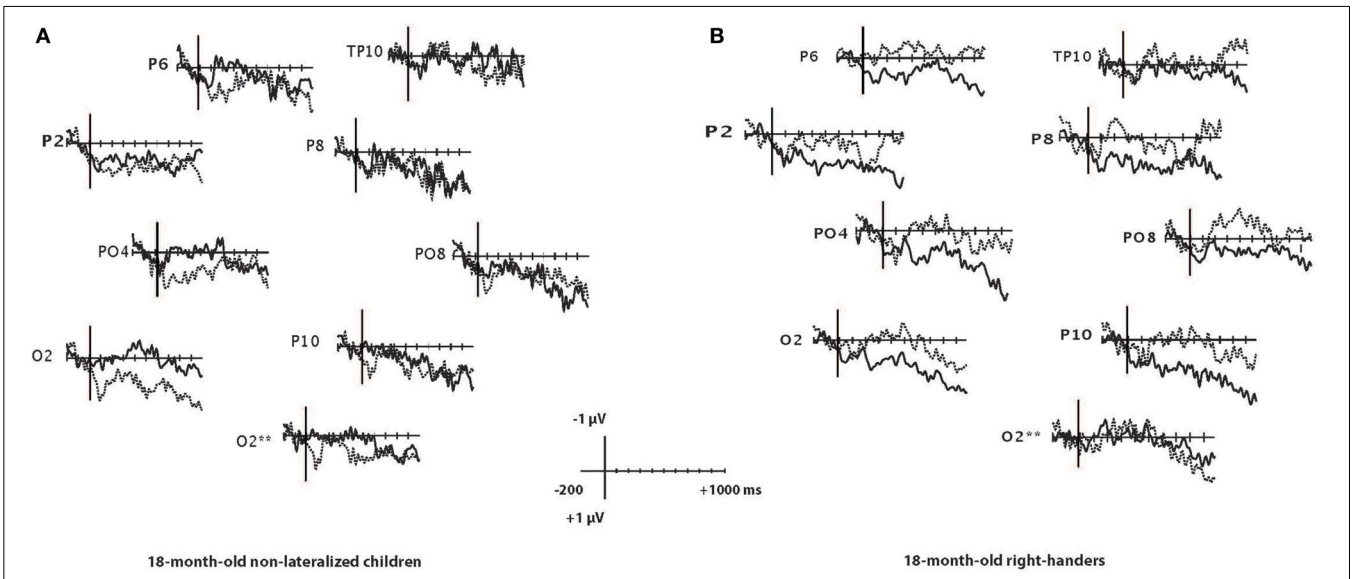


FIGURE 2 | (A,B) Grand-averaged waveforms for related (solid line) and unrelated (dashed line) target words in 18-month-old right handers **(A)** and non-lateralized **(B)** children over the right parietal-occipital recording sites. According to the 10–10 international system of electrode positions, channels 40 and 44 are both indicated as O2. The O2** reflects channel 44. The vertical line illustrates the target word onset.

Table 2 | N400 effect (in μV) over the right hemisphere as a function of vocabulary and handedness.

	18-months low voc.	18-months high voc.	24-months low voc.	24-months high voc.
Right-handers	−1.13 (0.9, $N = 2$)	−3.9 (3.5, $N = 5$)	0.48 (3.7, $N = 4$)	−1.4 (1.9, $N = 6$)
Non-lateralized	2.3 (5.3, $N = 5$)	−1.39 ($N = 1$)	−0.4 (1.6, $N = 2$)	−6.7 (0.06, $N = 2$)

DISCUSSION

The goal of this study was to investigate whether handedness and the occurrence of right-distributed N400 effect in a semantic priming task are related in 18- and 24-month-old children of low vs. high level of vocabulary. Our results showed *a significant relationship between handedness and level of vocabulary* in 18-month-olds. At that age, the proportion of children with a high vocabulary was greater among right-handers than among non-lateralized children. This is in line with evidence obtained in a recent study showing that children who showed consistent right-handedness between 6 and 14 months of age had more vocabulary at the age of 24 months than children whose handedness was expressed later (Nelson et al., 2014).

In our study, at 24 months, the non-lateralized children did not differ significantly from the right-handers for vocabulary. This may indicate that being right-handed (or having a preferred hand, more left-handers should be tested) early in life may be associated with a more precocious development of vocabulary, but that right-handedness *per se* has not a lasting influence on the level of vocabulary.

The greater percentage of right- than left-handers in our sample and also its slight (but non-significant) increase with age is in accordance with previous findings (Cochet et al., 2011; Jacquet et al., 2012). It has been found that handedness is already evident at 18 months, even though the percentage of non-lateralized participants at that age is higher than that of adults (Fagard, 2013) and even though there are large fluctuations in infants hand preference (Fagard, 1998; Corbetta and Thelen, 2002).

We also found *a relationship between the right-hemisphere distributed N400 effect and handedness* in 18-month-olds. The occurrence of the N400-like response in children has earlier been associated with incongruence detection in a picture-word context (e.g., Friedrich and Friederici, 2004; Torkildsen et al., 2006) and with semantic priming (Torkildsen et al., 2007; Rämä et al., 2013). It has been shown that there is a strong relationship between early word acquisition and generation of N400 response in developing brain (Friedrich and Friederici, 2010). Recently, the N400 effect was found even in 6-month-olds after few exposures of novel object-word combinations, suggesting that the mechanisms of N400 are mature already very early in infancy (Friedrich and Friederici, 2011). In the current study, the right-handed 18-month-olds had significantly more pronounced N400 effect than the non-lateralized 18-month-olds. The influence of handedness and vocabulary size on the amplitude of the N400 effect in 18-month-olds may be confounded since there is a link between them. Disentangling them was limited by the fact that there was only one 18-month-old who, at the same time, was non-lateralized and had a high vocabulary. However, the *post-hoc* comparisons of the N400 effect in 18-month-old right-handed children with either a low or a high vocabulary showed that the difference was not significant ($p = 0.34$), and the same was observed when comparing 18-month-old non-lateralized children with either a low or a high vocabulary ($p = 0.33$). This means that level of vocabulary alone cannot account for the larger amplitude of the N400 effect in 18-month-old right-handers. Similarly, the *post-hoc* comparisons of the N400 effect in 18-month-olds with a low vocabulary showed that the difference between right-handed and non-lateralized children was not significant ($p = 0.24$), and the same was observed when comparing 18-month-olds with a high vocabulary as a function of handedness ($p = 0.50$). This means that handedness alone cannot account for the variation of amplitude of the N400 effect. The group exhibiting the largest N400 effect included children who were right-handed and had a high level of vocabulary and the group who lacked the N400 effect included children who were not lateralized and had a low level of vocabulary. Thus, the relation between handedness and right-hemisphere N400 effect at 18 months seems to be partly, but not completely, mediated by the level of vocabulary.

At 24 months, there was no significant difference in the amplitude of the N400 effect between right-handed and non-lateralized children when vocabulary was not considered. No main effect of vocabulary had been observed in the previous study at that age (Rämä et al., 2013). Here we show that the N400 effect was significantly larger in the non-lateralized children with high vocabulary than in the right-handers with low vocabulary. Thus, at 24 months, there was no association between right-handedness and right-hemisphere N400 semantic priming effect, but vocabulary skills may still influence right-hemisphere N400 semantic priming effect in non-lateralized children. More data would be needed to confirm this.

The relation between the right-lateralized N400 effect and the level of vocabulary has been previously shown, even in 12-month-olds, as mentioned in the introduction (Friedrich and Friederici, 2004, 2010; Torkildsen et al., 2006). All these results, including ours, suggest that infants, as long as they have developed a certain level of productive vocabulary skills, demonstrate a similar asymmetrical N400 distribution than older children and adults (Bentin et al., 1985; Kutas et al., 1988; Van Petten and Luka, 2006; however, see Kutas and Hillyard, 1980, or Ressel et al., 2008; Spironelli and Angrilli, 2009, for different results concerning the asymmetry of N400 in adults). In all these infant studies of the N400 effect, handedness was never reported.

To our knowledge, this is the first ERP study to report a transitory relation between the N400 priming effect, vocabulary skills, and handedness in 18-month-old children. This period of age is characterized by the vocabulary "spurt," known to occur during the second year of life when an important increase in word production is observed (e.g., Bloom, 1973; Reznick and Goldfield, 1992). Our results indicate that both handedness and vocabulary skills contribute to the occurrence of the N400 effect during a semantic priming task at 18 months, showing for the

first time a link between handedness and language lateralization in infants.

How can we interpret the link between handedness and language lateralization? Since our results, like the previous ones already mentioned, support the notion that language is lateralized from its start, the same hypotheses that were evoked for the link between handedness and language development could in theory be applied here. The link between handedness and language development has been interpreted as reflecting the reorganization of hemispheric specialization (Ramsay, 1984), and as expressing the role of the left hemisphere in both language and right-handedness (Nelson et al., 2014). Does it mean that handedness is favored by lateralized language development or, alternately, that lateralized language development is triggered by the emergence of handedness? Here we cannot make the hypothesis that 18 month-olds are right-handed because of high vocabulary skills and right-distributed N400 effect since there are signs of handedness already *in utero* (Hepper et al., 1991), and since right-handedness predicts vocabulary skills later on (Nelson et al., 2014). Alternately, some argue that right-handedness may give an advantage for creating symbolic representations which is expressed by an ability to manage simultaneously multiple objects, an ability which is more developed in consistent right-handed infants than in inconsistent-handed infants (Kotwica et al., 2008), and that may favor language development (Nelson et al., 2014). The fact that neither the level of vocabulary or right-handedness alone did guarantee a significant N400 effect at the age of 18 months in our study may indicate that both high vocabulary skills and right-handedness reflect a lateralization advantage, without one being the cause of the other. In addition, the fact that we found a right-hemisphere language function to be more developed at 18 months in right-handers than in non-lateralized children may show that a more general lateralization effect is involved rather than only left-hemisphere facilitation. This is interesting to relate to a recent study showing a link between the density of gray matter in the right hippocampus at 7 months and expressive language skills at 12 months (Can et al., 2013).

In conclusion, our results confirm a link between the development of right-handedness and vocabulary skills and show a link between right-handedness and language lateralization at 18 months. We propose that the emergence of right-handedness and of right-distributed lexical-semantic processing, rather than being causally related one way or another, both reflect a general tendency to recruit the two hemispheres in a lateralized manner. The lack of relationships at 24 months may indicate that the relation between right-handedness and language lateralization at an earlier age does not correspond to a direct causal relationship.

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Perceptual asymmetries and handedness: a neglected link?

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Healthy individuals tend to weigh in more the left than the right side of visual space in a variety of contexts, ranging from pseudoneglect to perceptual asymmetries for faces. Among the common explanations proposed for the attentional and perceptual advantages of the left visual field, a link with the prevalence of right-handedness in humans has never been suggested, although some evidence seems to converge in favor of a bias of spatial attention toward the region most likely coincident with another person's right hand during a face-to-face interaction. Such a bias might imply an increased efficiency in monitoring both communicative and aggressive acts, the right limb being more used than the left in both types of behavior. Although attentional and perceptual asymmetries could be linked to right-handedness at the level of phylogeny because of the evolutionarily advantage of directing attention toward the region where others' dominant hand usually operates, it is also legitimate to question whether, at the ontogenetic level, frequent exposure to right-handed individuals may foster leftward biases. These views are discussed in the light of extant literature, and a number of tests are proposed in order to assess our hypotheses.

Keywords: perceptual and attentional asymmetries, handedness, left face bias, face, body

As largely shown by past research, healthy individuals tend to weigh in more the left than the right side of visual space in a variety of contexts, ranging from pseudoneglect (for a review, see Jewell and McCourt, 2000) to perceptual and attentional asymmetries for faces (e.g., Burt and Perrett, 1997; Hsiao and Cottrell, 2008). Among the common explanations provided for the existence of such attentional and perceptual advantages of the left visual field, including hemispheric asymmetries for processing faces (Bentin et al., 1996; Kanwisher et al., 1997; Yovel et al., 2008; Prete et al., 2013), spatial information (Mesulam, 1981; Corbetta and Shulman, 2002), and social information (Brancucci et al., 2009), a possible functional link between leftward biases and the prevalence of right-handedness in human population has never been proposed, beyond a bulk of correlational studies. In fact, while it is controversial whether the right-hemispheric specialization for face processing drives the leftward bias for faces or vice versa (Dundas et al., 2012b), no one has attempted to relate such a bias to the potential advantage of better monitoring others' dominant hand. In fact, it should be noted that the region of a person's right hand and limb, with respect to an observer facing that person (assuming a face-to-face interaction), falls in the observer's left field of view, so that any leftward bias would drive the focus of attention on the most active side of others' body.

In other words, it could be not by chance that the location in space of others' right hand, from the point of view of the observer, coincides with the well-known leftward bias of spatial attention, usually indicated as pseudoneglect (Bowers and Heilman, 1980; Jewell and McCourt, 2000). This is a natural property of attention whereby the left side of visual space is more relevant than the right side, as witnessed by the more frequent leftward errors made in bisection tasks (e.g., dividing a line or a rod into two halves), or by the fact that judgments on brightness, numerosity, and size are similarly skewed in favor of the left hemispace. A similar advantage for the left side is also observed in face perception, consisting in a preferential reliance upon the features on the left side of an observed face, when one has to make judgments about gender, attractiveness, age, and emotional expression conveyed by that face (Burt and Perrett, 1997). This is also reflected in the higher frequency of eye movements directed to the left side of the face (Butler et al., 2005). Given their biological relevance and their indivisibility from body – and thus from arms – in ecological settings, faces offer the best subject of inquiry to test our hypothesis.

WHICH ARE THE POTENTIAL ADVANTAGES OF LEFTWARD ASYMMETRIES?

We believe that a bias of spatial attention toward the region most likely coincident with others' right hand might have a deeply rooted justification in the communicative advantage conferred by attending to the limb most frequently used in gesturing, above all by right-handers and during speech (Kimura, 1973a,b; Dalby et al., 1980; Lavergne and Kimura, 1987; Saucier and Elias, 2001). Furthermore, the left-sided attentional bias might ensure a more efficient monitoring of aggressive behavior, the right limb being more used than the left also in violent actions (Coren and Porac, 1977). The other side of the coin is that a reduced monitoring of the right side of space – the space in which falls the dominant hand of encountered left-handed individuals – could contribute to the "surprise effect" at the basis of the left-handers' advantage in fighting and sports (Raymond et al., 1996).

Clearly, this line of argument holds for right-handed subjects in the role of observers, and to some extent one would predict that it should also hold for left-handed observers, at least on the basis of visual experience. For example, Hagemann (2009) found that the directions of tennis strokes performed with the right hand were easier to predict compared to those performed with the left

hand, regardless of observers' handedness. Similarly, Marzoli et al. (in preparation) observed that, when required to report the perceived orientation (front or back view) of pictures of ambiguous human silhouettes performing one-handed manual actions, both right- and left-handers perceived the figure more frequently in an orientation congruent with a movement performed with the right rather than the left hand. However, one should not forget the possible contribution of motor representations in shaping attentional biases. In fact, the left hemispatial bias for face processing usually observed in right-handers is absent (Jaynes, 1976; Heller and Levy, 1981; Roszkowski and Snelbecker, 1982; Hoptman and Levy, 1988) or weaker (Luh et al., 1994) in left-handers. Moreover, left-handers turn out to be less affected by a leftward pseudoneglect (Brodie and Dunn, 2005; see also the meta-analysis by Jewell and McCourt, 2000). In support of a role of hand-related motor representations, attention has been reported to be biased toward the right and left side of observed bodies, regardless of their spatial orientation, respectively, in right- and left-handers (Gardner and Potts, 2010; see also Zartor et al., 2010). Analogous effects of handedness have been reported by our own group for the imagination of others' actions (Marzoli et al., 2011a,b, in preparation). Noteworthy, these results seem to be in line with our proposal of a link between well-known attentional and perceptual leftward biases and an attentional bias toward the right side of others' body, such biases being affected in similar ways by handedness. However, we point out that viewing perspective seems to interact with motor experience as regards attentional asymmetries toward others' body, yielding a specific pattern of results (Marzoli et al., 2011a): when an actor is imagined as seen from the front, right-handers' attention is biased toward their own dominant hand (that is, toward the left from their own point of view), whereas left-handers' attention is biased toward their own non-dominant hand (that is, toward the left from their own point of view) or not biased at all; when an actor is imagined as seen from the back, both right-handers' and left-handers' attention is biased toward their own dominant hand (that is, toward the left from left-handers' point of view and toward the right from right-handers' point of view). Likewise, handedness does not affect perceptual and attentional asymmetries in the same direction in all tasks: form recognition and dot localization do not elicit any visual field difference between right- and left-handers, whereas letter recognition is performed better in the right visual field by right-handers, but not by left-handers (Bryden, 1973).

DEVELOPMENTAL TREND IN THE LEFT FACE BIAS: IS THERE A ROLE FOR EXPERIENCE?

In our opinion, the role of experience in the establishment of perceptual asymmetries in face processing deserves in-depth investigation. For example, the direction of reading and writing systems that characterize the various human cultures (left-to-right or right-to-left) has been called into cause as a possible factor modulating the leftward lateral bias for face exploration and attention (Vaid and Singh, 1989; Sakhuja et al., 1996; Heath et al., 2005; Megreya and Havard, 2011). Therefore, we want to highlight how, although attentional and perceptual asymmetries could be linked to right-handedness at the level of phylogeny – because of the evolutionarily adaptive advantage of directing attention toward the region of visual space where others' dominant hand usually operates – it is also legitimate to question whether, at the ontogenetic level, frequent exposure to right-handed individuals may foster leftward biases.

In this regard, it should be stressed that, whereas the leftward bias in face perception is usually observed in children of about 5 years (e.g., Roszkowski and Snelbecker, 1982; Levine and Levy, 1986; Kolb et al., 1992; Failla et al., 2003; Workman et al., 2006; Aljuhanay et al., 2010; Taylor et al., 2012), it is often reported to increase with age and reach an adult-like level by the age of about 10 years (Chiang et al., 2000; Workman et al., 2006; Anes and Short, 2009; Balas and Moulson, 2011; Taylor et al., 2012; Watling and Bourne, 2013; for a review, see Watling et al., 2012). However, the use of different methods seems to provide data in favor of both earlier (e.g., eye tracking; Wheeler, 2010; Liu et al., 2011; Dundas et al., 2012b) and later (e.g., moving window technique; Birmingham et al., 2012) emergence of an appreciable leftward bias in face processing. Similarly, a developmental trend has been shown in studies on the right-hemispheric advantage for face processing (Reynolds and Jeeves, 1978), although it is not always observed, maybe because of procedural differences (Young and Ellis, 1976; Young and Bion, 1980). Further support to our proposal can be drawn from studies showing that a general leftward bias for both upright and inverted human faces, monkey faces, and objects in infancy becomes a specific leftward bias for upright human faces in adulthood (Guo et al., 2009), and that the increase in leftward bias is specific for human faces, which suggests its experience-dependent nature (Balas and Moulson, 2011). A leftward bias for attending human faces was also reported for laboratory-raised rhesus monkeys and domestic dogs (Guo et al., 2009; see Dahl et al., 2013 for congruent findings in chimpanzees). Interestingly, the bias was absent for monkey and dog faces in dogs, and we believe that the prolonged experience with right-handed humans could be a more plausible account for such a specificity compared to other interpretations (e.g., a right-hemispheric specialization for human but not dog faces in both humans and dogs). Although rhesus monkeys showed a leftward bias for both human and monkey faces, given that they were presented only with human and monkey faces but not with dog faces, it cannot be resolved whether such a result was due to their difficulty in differentiating between the two species, to their experience with right-handed monkeys and humans, or to a non-species-specific bias. However, there is some evidence of right-handedness at least in captive rhesus monkeys (Westergaard and Suomi, 1996), as well as in other primates such as chimpanzees, gorillas, and baboons (see Hopkins, 2006; Cochet and Byrne, 2013; Meguerditchian et al., 2013 for reviews). We point out that population-level right-handedness is observed more often in captive rather than wild primates, as well as for communicative gestures rather than non-communicative actions, which has been credited to interaction with humans (Cochet and Byrne, 2013; Meguerditchian et al., 2013). This could suggest a crucial role for social factors also in the emergence of the left face/left visual field bias observed during emotional processing in nonhuman primates (see Lindell, 2013 for a review). On the other hand, findings from animal studies should be considered with caution as regards the origin of the leftward bias for faces, given that several results are inconsistent with a crucial role of interaction with

humans even in domestic animals. For example, Racca et al. (2012) used emotional faces of both dogs and humans and found a more complex pattern of results compared to those of Guo et al. (2009), dogs showing a left gaze bias for conspecific negative expressions, a right gaze bias for conspecific positive expressions and no bias for conspecific neutral expression, as well as a left gaze bias for human negative and neutral expressions and no bias for human positive expressions. Moreover, sheep exhibit a left visual field advantage for conspecific (Peirce et al., 2000) but not for human faces (Peirce et al., 2001). Domestic chicks with no visual experience of human eyes and gaze also show a left visual field preference for monitoring a human-like dummy mask (Rosa Salva et al., 2007), which shows that even the emergence of leftward biases for human faces can be completely independent from interaction with humans.

The idea that the frequent interaction with right-handed individuals might promote leftward biases is consistent not only with both the experience-expectant and the experience-dependent view of brain development (Greenough et al., 1987), but also with previous studies showing that experience can affect the lateralization of face processing (e.g., infant holding biases; Vervloed et al., 2011; reading habits; Vaid and Singh, 1989; Sakhuja et al., 1996; Heath et al., 2005; Megreya and Havard, 2011). However, the fact that eye tracking studies reveal that a left visual field bias during face observation emerges within 9–11 months (Wheeler, 2010; Liu et al., 2011; Dundas et al., 2012b) and the fact that the leftward bias becomes more specific for upright human faces with increasing age (Guo et al., 2009) indicate that reading habits cannot account for the emergence of the bias. On the other hand, the cumulative experience with right-handed individuals might be responsible for the leftward bias increasing and becoming more selective with age. Moreover, given that the number of interactions with partners other than the primary caregiver increases with time, it should be investigated whether children of left-handed mothers show a shift from a rightward bias to a leftward one over time (in this regard, see Wheeler, 2010, who observed that in children aged 3–6 months with a rightward bias, this decreased with age).

The developmental trend in right-hemispheric specialization for faces has been credited to a parallel increase in right-hemispheric specialization for configural processing (Anes and Short, 2009). However, if the leftward bias for face processing is linked to configural processing, it should be noted that body configural information might include the knowledge (in terms of both first-order relational information and structural information; Reed et al., 2006) that the dominant hand of humans is usually placed on their right side, which could explain why face inversion, which disrupts configural processing (Maurer et al., 2002), also disrupts the leftward bias/right-hemispheric dominance in face processing (Ellis and Shepherd, 1975; Leehey et al., 1978; Luh, 1998; Coolican et al., 2008; Anes and Short, 2009; Bourne, 2011). The link between the leftward bias/right-hemispheric dominance and configural processing of faces is further corroborated by their similar developmental trends, configural processing and face-inversion effects also reaching adult-like levels by the age of 10 years (Carey and Diamond, 1977; Diamond and Carey, 1977; Mondloch et al., 2002), as well as by the finding that face-inversion effects appear to be stronger in the left rather than the right visual field (Leehey et al., 1978). In this regard, it is noteworthy that individuals with autism, who exhibit impaired configural processing (Behrmann et al., 2006), are less affected by both the face inversion effect (Hobson et al., 1988; Tantam et al., 1989) and the leftward bias for face processing (Dundas et al., 2012a; Taylor et al., 2012; see also Dundas et al., 2012b).

Another factor reported to affect the leftward bias for faces is maternal preferred cradling side: adults whose mother had an atypical right-side preference for holding infants show a reduced left-bias for chimeric faces compared to adults whose mother had the typical left-side preference (Vervloed et al., 2011). Interestingly, the maternal cradling side is also related to children's handedness, right-cradled infants having slightly higher odds of being left-handed at 19 months of age (Scola and Vauclair, 2010). Given that children seem to imitate handedness preferences of adults (Harkins and Michel, 1988; Harkins and Uźgiris, 1991; Michel, 1992; Fagard and Lemoine, 2006), imitation could also account for the greater incidence of left-handedness among right-cradled children, both because left-handed mothers are more likely to cradle on the right side (Scola and Vauclair, 2010) and because holding the infant on one side should free the opposite hand for other tasks (Huheey, 1977; see Hopkins, 2004 for similar associations between cradling side and hand preferences of both mother and infant in nonhuman primates). However, a reduced attentional bias toward the right arm might also explain the smaller leftward bias for faces observed in left-handers and in right-cradled individuals. This hypothesis deserves particular attention, above all in the light of the fact that individuals with autism, who show deficits in action imitation (see Williams et al., 2004 for a review), also exhibit a reduced leftward bias for face processing (Dundas et al., 2012a; Taylor et al., 2012; see also Dundas et al., 2012b) and a higher proportion of non-right-handedness (e.g., Escalante-Mead et al., 2003), which seems not to be accounted for by parental handedness (Tsai, 1982).

SPECIFITY vs. GENERALIZABILITY OF LEFTWARD BIASES

Some evidence indicates that adult humans exhibit a leftward bias for upright human faces, but not for several other classes of stimuli such as vases, landscapes, and fractals (Mertens et al., 1993; Leonards and Scott-Samuel, 2005). Leonards and Scott-Samuel (2005) proposed that the leftward bias might be specific to socially relevant stimuli, and this could be in line with studies suggesting that the more the emotional load of the stimuli or tasks, the greater the leftward bias for faces (Gallois et al., 1989; Coolican et al., 2008; Thompson et al., 2009). In line with this proposal, centrally presented gaze cues (i.e., social stimuli) facilitate the detection of spatially congruent targets presented in the left visual field (that is, the region of the observed person's right hand during a face-to-face interaction) but not in the right visual field, whereas arrow cues (i.e., non-social stimuli) are effective for targets presented in both visual fields (Marotta et al., 2012; see also Greene and Zaidel, 2011).

The role of social relevance in the emergence of attentional asymmetries in favor of the left visual field is corroborated by a series of studies by Mogg and Bradley (1999, 2002) showing that threatening faces induced a greater attentional capture compared

to happy and neutral faces when the faces were subliminally presented in the left but not in the right visual field, and that this effect was particularly apparent for more anxious individuals. A study by Field (2006) found a similar pattern of results, extending the leftward bias for threatening stimuli to a different population (children aged 7–9 years) and different stimuli (animals). Therefore, although the leftward bias/right hemispheric advantage could be more evident for faces, it is not exclusive of this class of stimuli, as also shown by studies generalizing the left visual field bias to photographs of houses and cars (Levine et al., 1984) and line drawings of common objects (Kim et al., 1990). Nonetheless, it is not unreasonable to hypothesize that more general attentional and perceptual asymmetries may arise from an initial leftward bias for faces and/or bodies. Specifically, given that human bodies and faces are the most ecologically relevant and likely the most recurrent stimuli people deal with in everyday life, the asymmetrical processing they elicit could generalize to some extent to other domains. This view would be consistent with the observation that handedness and sex seem to affect the left side bias for faces and other leftward asymmetries in similar ways: according to a meta-analysis of line bisection studies conducted by Jewell and McCourt (2000), in fact, males show a slightly larger pseudoneglect compared to females and right-handers show a slightly larger pseudoneglect compared to left-handers. Interestingly, this latter finding cannot be attributed to the mere use of the left hand, because the authors also mentioned a relative bias in the direction of the hand used to perform bisection, which is consistent with the activation-orientation theory of Kinsbourne (1970). On the contrary, the modulation of pseudoneglect by handedness could match the way in which one's own motor representations seem to affect attentional asymmetries toward humans bodies observed from the front (e.g., Gardner and Potts, 2010; Marzoli et al., 2011a). Finally, the fact that pseudoneglect shows a developmental trend similar to that of the leftward bias for faces also suggests their related origin (Bradshaw et al., 1988; Dellatolas et al., 1996; Failla et al., 2003). However, it should be noted that a left-sided visuospatial bias has also been found in birds (Diekamp et al., 2005), and embryonic light stimulation has been invoked for its emergence (Chiandetti, 2011), which suggests that pseudoneglect could arise from causes other than the social ones.

EMOTIONAL ASYMMETRIES

On the basis of the literature reviewed in the previous section, social stimuli, and emotional stimuli in particular, are more likely to induce attentional and perceptual asymmetries compared to non social stimuli. In this section, we attempt to conciliate the larger asymmetries observed for emotional stimuli with our main hypothesis. As recently stressed by Watling et al. (2012), future research should address the advantages of lateralization for emotion processing, as well as related gender differences. In this regard, a positive correlation has been observed between children's left hemispatial advantage for emotion perception and their ability to understand emotional states in cartoon situations and in eyes (Workman et al., 2006), as well as in faces, although this was shown only in male children (Watling and Bourne, 2013). However, a recent study extended the positive correlation between left-lateralized processing and performance to the discrimination of both human and chimpanzee faces in both species (Dahl et al., 2013). These studies suggest a link between the lateralization of emotional processing and the understanding of others' emotional/cognitive states, which is bolstered by their similar time course, theory of mind emerging by the age of 4 years and improving during childhood (Baron-Cohen, 1995). Moreover, the leftward bias for faces approaches adult-like levels by the age of 10 years (Chiang et al., 2000; Workman et al., 2006; Anes and Short, 2009; Taylor et al., 2012), just before children start to exhibit a preference for the left eye (from the observer's viewpoint) during face scanning (Birmingham et al., 2012) and a patent improvement in their ability to interpret emotion from eyes (Tonks et al., 2007).

Therefore, one could wonder whether the advantage of the right-hemispheric specialization for emotion processing might lie in monitoring other's emotional states and their subsequent actions within the same hemisphere, and whether leftward biases could be strengthened by the fact that interaction partners' facial expressions and eye movements are constantly associated with their right-handed actions. This hypothesis deserves particular consideration, given that the leftward bias for emotion processing could appear counterintuitive, emotions being expressed more intensely on the left side of the face, which falls in the right visual field of the observer in a face-to-face interaction (Sackeim and Gur, 1978). On the other hand, there is some evidence that anger might be expressed more intensely on the right side of the face (Indersmitten and Gur, 2003) and that the leftward bias might be larger for anti-social emotions (and in particular for anger) than for pro-social emotions (Workman et al., 2000). Thus, the leftward bias appears to be less counterintuitive if one assumes that both bearing a particular sensitivity to the hemiface expressing more intense threat-related facial displays and directing attention toward the region containing the right arm of an angry individual could provide important ecological advantages. This could be particularly true during interactions among males, and we would like to point out that the leftward bias has been reported to be stronger in males than in females (Bourne, 2008; see also Godard and Fiori, 2010). Moreover, in males the leftward bias reaches its highest degree when they observe male faces expressing anger rather than male faces expressing the other five basic emotions or female faces expressing all basic emotions (Rahman and Anchassi, 2012). The uniqueness of anger among emotions has already been proposed by Indersmitten and Gur (2003; see Workman et al., 2000 for similar considerations), who stressed both its nature of evolutionarily important sign for action (its purpose is to prepare the organism for conflict) and its increased likelihood to be appreciated by the perceiver (its greater intensity on the right rather than the left hemiface enhances its impact on the hemisphere more dominant in emotion processing). In the same vein, it is not surprising that more anxious individuals exhibit a greater leftward bias compared to less anxious ones (Heller et al., 1995; Keller et al., 2000; Voelz et al., 2001; Bourne and Vladeanu, 2011), and therefore an interesting experimental question is whether the former also show greater attention toward the right limbs of human bodies compared to the latter.

We would like to remark that the advantages of lateralization for emotion processing discussed in this section are in agreement

with previous suggestions (e.g., Vallortigara and Rogers, 2005) that (i) the lateralization of cerebral functions enhances cognitive capacity and efficiency (a positive correlation existing between the leftward bias for emotion perception and performance in emotion discrimination), and (ii) the alignment of the direction of behavioral asymmetries at the population level emerges, as an evolutionary stable strategy, under social pressures (the leftward bias for emotion processing being credited to the advantage of monitoring others' emotional states and their dominant hand within the same hemisphere).

COUPLING BETWEEN FACE AND BODY PROCESSING

Our proposal that the leftward bias for faces might be associated with a similar bias for bodies is supported by several analogies between face and body processing, including the importance of configural information, the inversion effect affecting both categories (e.g., Reed et al., 2003), and embodied experience, humans being able to move both faces and bodies (Slaughter et al., 2004). On the other hand, face and body representations are likely to differ at least to some extent (e.g., Soria Bauser et al., 2011). Moreover, although both face and body processing develop early in infancy, there is some evidence that face expertise may precede body expertise (Heron-Delaney et al., 2011; Slaughter et al., 2002). A possible account for such a differential development is that the earliest social experiences between infants and caregivers involve a face to face interaction, so that infants are exposed more often to faces than to whole bodies. Surely, face and body representations interact reciprocally (van de Riet and de Gelder, 2008; Yovel et al., 2010; Aviezer et al., 2012) and also induce similar responses (Tamietto et al., 2009).

At the neural level, the same area, the right fusiform gyrus, contains representations for both faces (Kanwisher et al., 1997) and bodies (Peelen and Downing, 2005). Although largely overlapping (Peelen and Downing, 2005), the fusiform face and body areas (FFA, FBA) turned out not to be identical (Schwarzlose et al., 2005; Peelen et al., 2006). Given that the magnitude of the asymmetry of the FFA strongly correlates with leftward asymmetries in face perception (Yovel et al., 2008), the existence of a similar association between FBA and perceptual and attentional asymmetries toward the right side of human bodies deserves investigation. Moreover, whereas the size and selectivity of the rFFA increase with age (Aylward et al., 2005; Golarai et al., 2007; Scherf et al., 2007; Peelen et al., 2009), matching the developmental trend of face-related configural processing and leftward bias, those of the rFBA do not differ between children and adults, this region not showing any development beyond the age of 7 years (Peelen et al., 2009). Thus, given that the age-related increase of the leftward bias for faces can be explained also in terms of the mere maturation of the biological substrate, it could be investigated whether an age-dependent increase in the attention allocated to the right side of human bodies exists and, if so, whether it pre-exists that observed for faces. According to Peelen et al. (2009), a possible account for the differential development of rFFA and rFBA is that young children, when not looking up, usually observe the bodies rather than the faces of older (and thus taller) individuals, whereas adults are more likely to observe the faces of other individuals. For the same reason, the dominant hand might be associated earlier to the right side of bodies rather than of faces, which could contribute to explain why the rFBA reaches adult size before the rFFA. The FFA is also more right-lateralized in right-handers than in left-handers (Willems et al., 2010), in line with the weaker left face bias observed in left-handers. Although less consistent, similar effects of handedness have been reported for the FBA (Willems et al., 2010), which could be linked to the weaker bias toward the right side of bodies observed in left-handers (Gardner and Potts, 2010; Marzoli et al., 2011a,b, 2013).

CONCLUSION AND FUTURE DIRECTIONS

Although different adaptive reasons have been proposed for the evolution of human right-handedness (Cochet and Byrne, 2013), the adaptive functions of the left face bias, as well as, broadly speaking, perceptual, and attentional asymmetries, have not received the same consideration. The present article attempts to provide a contribution in this direction, suggesting several research questions. The first prediction derived from our hypothesis is that the intensities of the leftward bias for faces and for bodies should be correlated. The leftward bias for bodies could also be modulated by the same factors affecting the leftward bias for faces, such as maternal cradling preference, age, anxiety, emotional context (for example, the presentation of angry faces or voices should increase the bias), configural processing (the bias should be reduced by inversion), and so on.

Moreover, a major topic of investigation should be the effect of experience with right-handed individuals in inducing leftward biases (for both faces and bodies). For example, it could be expected that the bias would be stronger for faces and bodies of highly familiar right-handed individuals than for faces and bodies of unfamiliar individuals. In the same respect, the discovery that dogs show a selective left face bias for human faces (Guo et al., 2009) offers an interesting opportunity to investigate the role of experience also in a nonhuman species. Specifically, it could be tested whether the bias is weakened, or even reversed, in dogs that have interacted mainly with left-handed individuals (i.e., owners, breeders, trainers). Such a study would provide useful information on the contribution of sensory experience in the manifestation and perhaps even in the origin of a perceptual asymmetry whose existence is known since several decades in human beings, but that has recently been observed also in other species.

Finally, an important field of study could address the topic of leftward biases in individuals with autism, who exhibit deficits in social communication (Klin et al., 2003) and emotion recognition from both faces and bodies (Philip et al., 2010), as well as in inferring others' complex mental states from faces and particularly by eyes (Baron-Cohen et al., 1997). These individuals are known to show impaired configural processing (Behrmann et al., 2006) and an absent (Dundas et al., 2012a) – or at least delayed (Taylor et al., 2012) – perceptual bias for the left side of faces. Given the link between face and body representations, it should be investigated whether in this population the reduced leftward bias for faces is coupled with a reduced leftward bias for bodies, just as a reduced face-inversion effect (Hobson et al., 1988; Tantam et al., 1989) is coupled with a reduced body inversion effect (Reed et al., 2007). Moreover, it would be interesting to examine whether

action imitation deficits of individual with autism are positively related to non-right-handedness and negatively related to leftward biases toward faces and bodies. If so, a reduced attention toward the right side of human bodies could be responsible for the abnormal pattern of behavioral asymmetries in the autistic disorder, endorsing once again the role of body representations in social cognition.

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Degree of handedness, but not direction, is a systematic predictor of cognitive performance

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A growing body of evidence is reviewed showing that degree of handedness (consistent versus inconsistent) is a more powerful and appropriate way to classify handedness than the traditional one based on direction (right versus left). Experimental studies from the domains of episodic memory retrieval, belief updating/cognitive flexibility, risk perception, and more are described. These results suggest that inconsistent handedness is associated with increased interhemispheric interaction and increased access to processes localized to the right cerebral hemisphere.

Keywords: handedness, interhemispheric interaction, episodic memory, belief updating, cognitive flexibility

INTRODUCTION

Psychological research examining "individual differences" grounded in biology (in contrast with, for example, personality/temperament, or in experience) typically focuses on sex and age. Another biologically based dimension of individual differences, handedness, has received much less attention. This neglect has arisen in part because handedness research has largely been the province of neuropsychologists, and such research makes little contact with the methods and theories of mainstream psychology. This lack of contact is the product of both the idiosyncratic methods employed in handedness research (e.g., lateralized presentation of input), and the fact that, historically, research attempting to identify key functional and structural differences between left- and right-handers has produced equivocal results (other than the fact that brain asymmetry appears to be weaker and more variable in left-handers).

The purpose of this article is to acquaint the reader with a growing body of evidence identifying handedness as a robust predictor of individual differences across a number of domains. The research to be reviewed breaks with past handedness research in a critical way: instead of comparing left- versus right-handedness, it focuses on comparisons between consistent/strong-handers (CH) and inconsistent/mixed-handers (ICH). Here, we define CH as using the dominant hand for virtually all common manual activities, and ICH as using the non-dominant hand for at least one common manual activity. That is, historically, research examining individual differences in handedness focused on the effects of *direction* of hand preference on behavior, thereby comparing left versus right-handers. However, evidence has accumulated that the critical dimension on which the handedness groups differ is in *degree* (consistent versus inconsistent) of hand preference. That is, how consistently, or strongly, an individual prefers to use one versus the other hand over a wide variety of tasks may be the more appropriate indicator of cerebral organization and of behavior. In fact, we would argue here that a major reason why previous research has failed to clearly determine individual differences in handedness effects on behavior is because the measure used to define handedness has heretofore been incorrect. Instead of *direction* of hand preference being the variable of interest, it should be *degree*.

The distinction between consistent and inconsistent handedness is based on a simple median split on scores on the Edinburgh Handedness Inventory (Oldfield, 1971). Scores range from −100 (pure left handed) to +100 (pure right-handed). The population median, based on a large sample of 1595 subjects, is 80. Thus, inconsistent handedness is defined as handedness scores below 80, which is equivalent to performing at least one of the ten activities with the non-dominant hand. A summary of the population proportions of handedness is presented in **Table 1**.

There are two things to note about **Table 1**. First, right-handers tend to be consistent handed while left-handers are largely inconsistent handed. Second, consistent handedness is more prevalent among females than among males.

While it is beyond the scope of this chapter to fully explicate the mechanisms underlying the distinction between CH and ICH, key principles involve interhemispheric communication and functional access to right hemisphere processing. More consistent hand preference is associated with smaller corpus callosum size (e.g., Luders et al., 2010) and with decreased right hemisphere activation (e.g., Propper et al., 2012). Accordingly, consistent- versus inconsistent handedness is associated with decreased versus increased interhemispheric interaction and with decreased versus increased right hemisphere access, respectively. The following review will focus primarily on two task domains for which interhemispheric interaction and right hemisphere access have

Table 1 | Percentages of female and male participants, classified according to both direction and degree of handedness.

Direction of handedness	Degree of handedness		
	Strong	Mixed	
FEMALES			
Right	59.3	31.0	90.3
Left	3.2	6.5	9.7
	62.5	37.5	
MALES			
Right	47.8	41.6	89.4
Left	2.4	8.2	10.6
	50.2	49.8	

been implicated: episodic memory retrieval (associated with right frontal areas) and belief updating/cognitive flexibility (associated with right frontal-parietal areas), with the evidence showing that ICH exhibit superior episodic memory and increased belief updating/cognitive flexibility. Other related findings will also be presented. A summary of the findings reviewed is provided in **Table 2**.

We are not arguing that the reader should become a "handedness" researcher. Instead, we are encouraging researchers to include degree of handedness as a variable in their designs, much like many already do with sex and/or age. At the very least, including handedness as a variable in analyses would move variability out of the omnibus error term and into a specific effect term, thereby providing increased statistical power to detect other effects of primary interest. At best, systematic individual differences as a function of handedness and concomitant gradations in interhemispheric interaction and in right hemisphere access, could prove to be a useful construct in the development and testing of domain-specific theories.

HANDEDNESS AND MEMORY

Some of the most robust findings demonstrating the effects of handedness as an individual difference variable come from the domain of memory research. This work initially relied on predictions made by the Hemispheric Encoding and Retrieval and Asymmetry (HERA) model (Tulving et al., 1994). They reported that, for semantic memory tasks, brain activity at both encoding and retrieval were lateralized to the left hemisphere. In contrast, for episodic memory, activation at encoding versus retrieval was lateralized to the left versus right hemispheres, respectively. This finding raised the possibility that (i) episodic memory relies on interhemispheric interaction (necessary to integrate left hemisphere encoding with right hemisphere retrieval) to a greater extent than does semantic memory (left hemisphere encoding and retrieval); (ii) individual differences in interhemispheric interaction would be reflected in individual differences in memory ability, and (iii) individual differences in degree of hand preference, being associated with individual differences in interhemispheric interaction, would therefore also be associated with individual differences in memory performance. Specifically, inconsistently handed individuals, having increased interhemispheric interaction, possibly mediated via

Table 2 | Summary of research on handedness differences in memory.

Task	Findings	Citation
Free recall of words	ICH advantage	Propper et al. (2005)
Free recall of words	ICH advantage	Lyle et al. (2008a)
Free recall of words	ICH advantage	Christman and Butler (2011)
Free recall of events from own life	ICH advantage	Propper et al. (2005)
Recall of early childhood memories	ICH advantage	Christman et al. (2006b)
Paired-associate recall	ICH advantage	Lyle et al. (2008b)
Source memory (DRM paradigm)	ICH advantage	Christman et al. (2004)
Source memory (sensory modality)	ICH advantage	Lyle et al. (2008b)
Self-reported everyday memory	ICH advantage	Christman and Propper (2008)
Self-reported dream recall	ICH advantage	Christman (2007)
Incidental memory for deeply processed words	ICH advantage	Christman and Butler (2011)
Incidental memory for shallowly processed words	No difference	Christman and Butler (2011)
Know versus remember judgments	ICH: rem > know CH: rem = know	Propper and Christman (2004)
Word recognition	No difference	Propper and Christman (2004)
Word recognition	No difference	Lyle et al. (2008a)
Face memory	ICH advantage	Lyle and Orsborn (2011)
Implicit memory	No difference	Propper et al. (2005)
Semantic memory	No difference	Propper et al. (2005)
Memory for paragraphs	ICH advantage	Prichard and Christman (2012)
Openness to persuasion	ICH more open	Christman et al. (2008)
Gullibility	ICH more gullible	Christman et al. (2008)
Belief in evolution	ICH more likely	Niebauer et al. (2004)
Magical ideation	ICH have higher levels	Barnett and Corballis (2002)
Cognitive dissonance	ICH have higher levels	Jasper et al. (2009)
Placebo effect	Larger in ICH	Christman et al. (2006a)
Anchoring effect	Larger in ICH	Jasper and Christman (2005)
Counterfactuals	ICH produce more	Jasper et al. (2008)
Ambiguous figures	ICH higher reversal rate	Christman et al. (2009)
Ambiguous words	Greater activation in ICH	Sontam and Christman (2012)
Musical preferences	Greater preference for obscure genres in ICH	Christman (2013)
Sensation seeking	Higher levels in ICH	Christman (2011a)

(Continued)

Table 2 | Continued

Task	Findings	Citation
Consumer loyalty	Lower levels in ICH	Lanning and Christman (2010)
Right Wing Authoritarianism	Lower levels in ICH	Christman (2008)
Sense of disgust	Stronger in CH	Christman (2012)
Risk perception	ICH more loss averse	Christman et al. (2007b)
Sunk cost effect	Higher levels in ICH	Westfall et al. (2012)
Taking others' perspectives	ICH are better	Sontam et al. (2005); Lanning and Christman (2010)
Sleep architecture	ICH: shorter latency, increased time in NREM	Propper et al. (2007)

ICH, inconsistent handed; CH, consistent handed.

greater corpus callosal connectivity, would demonstrate superior episodic, but not semantic, memory.

Supporting the hypothesis, Propper et al. (2005) found that ICH outperformed CH on an episodic memory task involving word list recall. Interestingly, there was no significant difference between the handedness groups on a word fragment completion task used as a test of semantic memory. Handedness differences are not typically found in recognition memory; however, in another test of episodic memory (e.g., Christman and Propper, 2001), Propper and Christman (2004) found that, despite equal levels of recognition memory, ICH are more likely to report explicitly episodically "remembering" an item while CH are more likely to report merely semantically "knowing" that they saw the item before.

The findings that ICH have superior episodic recall abilities and show a greater tendency than CH to make "remember" judgments raises the possibility that handedness differences in episodic memory may reflect underlying differences in source memory. Three findings examining handedness differences in false alarms, using both laboratory based and real-world memories, support this notion. First, Christman et al. (2004) demonstrated that ICH are less likely to report having a false memory for the critical lure in by the Roediger and McDermott (1995) paradigm, suggesting that the source of memories may be more available in the ICH relative the CH. Second, Lyle et al. (2008b) tested source memory for words that participants had originally either read or heard; again, relative to CH, ICH were better at remembering whether the original presentation of items has been visual or auditory. Finally, Lyle et al. (2008a) also reported fewer false alarms in ICH.

These "snapshot" handedness effects on memory-that is, of superior episodic memory among ICH relative to CH— have been extended in investigations of handedness and memory effects across the lifespan. Christman et al. (2006b) reported that ICH experience an earlier offset of childhood amnesia, and therefore a younger age for their earliest childhood memory. Lyle et al. (2008b) obtained an ICH advantage on a recall task in a sample of middle aged adults, but not with a sample of older adults. Lyle et al. (2008b) proposed that as people age, the corpus callosum degenerates, thus attenuating the ICH advantage. Specifically, the decline in memory from middle- to older-aged adults was larger in the ICH, consistent with a callosal contribution to episodic memory. Finally, Kempe et al. (2009) found that ICH were more easily able to acquire foreign vocabulary words in adulthood. Although vocabulary recall in adulthood may involve both episodic and semantic memory processes, this finding suggests that individual differences in handedness may account for some between individual variability in language acquisition.

Findings of superior episodic memory in ICH relative the CH extend beyond artificial, laboratory information. For example, Propper et al. (2005) demonstrated an ICH advantage for autobiographical, self-reported events that occurred outside the laboratory, and Christman et al. (2006b) reported an ICH advantage for earliest childhood memories. Christman and Propper (2008) found that ICH reported fewer memory problems in everyday life, especially in the domains of task monitoring and conversation. Christman (2007) reported that ICH remember more dreams and report more frequent déjà vu experiences. Prichard and Christman (2012) found that the ICH advantage in memory extends to recall of paragraph-level material, although the ICH advantage was larger for males than for females. Finally, Lyle and Orsborn (2011) reported superior face memory in ICH.

It is important to point out that in the studies reviewed above, most compared ICH with consistent *right*-handers. Given that consistent-left-handers are only about 1–3% of the population (Lansky et al., 1988), studies comparing ICH with consistently right and consistently left handed individuals are time consuming, difficult to conduct, and therefore infrequent. However, Lyle et al. (2012) collected a large sample of consistent-left-handers in order to determine whether it is consistent handedness *per se* that is associated with less or episodic memory, or if this effect is specific to consistent-*right*-handedness. Importantly, ICH outperformed CH, on an episodic memory task, regardless of the *direction* of CH hand preference; that is, regardless of whether CH were left- or right-handed, ICH performed better.

HANDEDNESS AND BELIEF UPDATING/COGNITIVE FLEXIBILITY

Ramachandran (1995) hypothesized that the left hemisphere is important for maintaining our current beliefs about the world, while the right hemisphere acts as an anomaly detector and is sensitive to information inconsistent with those beliefs. This suggests a possible role for interhemispheric connectivity in the belief updating process. When something challenges pre-existing beliefs, it may be the right hemisphere's job to notice the inconsistency and communicate it to the left hemisphere. Since belief updating may be considered, more broadly, an example of cognitive flexibility, further studies have also looked at numerous DVs which, taken together, may be considered measures of cognitive flexibility. It is to the literature investigating a possible relationship between handedness and belief updating/cognitive flexibility which we now turn.

Niebauer et al. (2004) found that consistent-handers are more likely to report holding young-earth creationist beliefs. The authors argued that, because children typically hold creationist views at some point (Evans, 2000), the retention of such beliefs is the result of a failure to update beliefs about human origins in light of new evidence. Similarly, Christman et al. (2008) reported that ICH are more open to persuasion. At the same time, however, they found that ICH were also more gullible, showing greater susceptibility to the "Barnum effect." This finding may be related to that of Barnett and Corballis (2002), who reported that ICH were more prone to magical ideation (i.e., beliefs in ESP, UFOs, astrology, etc). Thus, CH are more resistant to belief updating, and are therefore less likely to alter their views based on little evidence.

Once researchers obtained the basic finding that degree of handedness predicts the tendency to update one's beliefs or, to frame it differently, degree of handedness predicts resistance to information challenging pre-existing beliefs, the handedness paradigm has been applied to several areas for which the belief updating/cognitive flexibility process is relevant. For example, it has been applied to cognitive dissonance (Jasper et al., 2009), who conducted a study in which participants were given false personality profiles. In the experimental condition, participants were told their profiles indicated high levels of sexism. When asked to judge a fictional sex based discrimination suit, ICH who had been told they were sexist awarded higher payouts than CH, indicating greater cognitive dissonance in ICH. Handedness differences have also been obtained in the magnitude of placebo effects, with ICH exhibiting much larger placebo effects than CH (Christman et al., 2006a). Thus, handedness may be a variable of interest for researchers examining how belief affects treatment outcomes, or for researchers who want to reduce the error term in clinical trials that necessarily include a placebo condition.

As stated at the beginning of the section, belief updating could arguably fall under the broader area of cognitive flexibility. The empirical evidence indicates handedness does indeed predict cognitive flexibility as measured by a surprising variety of DVs. Starting with research on basic heuristics, Jasper and Christman (2005) found that inconsistent-handers were less susceptible to anchoring on a task that asked participants 12 factual knowledge questions after exposing them to unhelpful high or low anchors. Resisting anchors in such a situation may require one to hold multiple representations, a process requiring considerable cognitive flexibility. In the area of counterfactual reasoning, Jasper et al. (2008) found that, when asked to come up with counterfactual alternatives to various scenarios, ICH produce more upward counterfactuals and downward counterfactuals. Research on more basic perceptual processes shows that ICH can more easily update their perception of ambiguous figures (Christman et al., 2009) and that ICH more readily fall for a sensory illusion in which a participant comes to "feel" taps on a fake arm (Niebauer et al., 2002). During investigations of semantic flexibility, ICH showed a greater tendency to switch between subcategories when asked to name as many animals as they could (Sontam et al., 2009) and had an easier time accessing "weak" associates of ambiguous stimulus words than consistent-handers did (Sontam and Christman, 2012). ICH have also been shown to be more creative, measured via divergent thinking, compared to CH (Shobe et al., 2009).

As with the handedness and memory paradigms, there has been an interest in whether these cognitive flexibility effects generalize beyond the realm of interesting experiments. What does it mean to say inconsistent-handers are more cognitively flexible outside of an experimental context? As it turns out, handedness predicts certain kinds of esthetic judgments, with ICH showing more appreciation for self-referential works by M.C. Escher (Niebauer and Garvey, 2004) and for a wider variety of musical genres (Christman, 2013) than CH. Further, consistent-handers are less sensation seeking (Christman, 2011a), exhibit greater consumer brand loyalty (Christman and Lanning, 2012), have greater disgust sensitivity (Christman, 2012), and score higher on measures of Right Wing Authoritarianism (Christman, 2008) than ICH.

Perhaps of the greatest practical relevance, the link between handedness and cognitive flexibility is of potential clinical relevance. Consistent-handers are more likely than inconsistent-handers to ruminate (Niebauer, 2004), to display eating disorder symptomatology (Christman et al., 2007a), and to show higher levels of body dysmorphia (Christman, 2011b).

MISCELLANEOUS HANDEDNESS FINDINGS

While the memory and cognitive flexibility literatures are the most well developed of the literatures investigating degree of handedness as an individual difference variable, it is worth mentioning several empirical studies that have branched out beyond these two major areas. Although much remains to be explained about what underlies the following findings, it is hoped that there will be something of interest to researchers from across the discipline of psychology.

Several studies looking at emotion and risk perception have uncovered evidence of handedness effects. Propper et al. (2010) reported that ICH demonstrated increased negative affect across a wide variety of emotional states, compared to CH, although only feelings of "anger" were significantly greater in ICH. Christman et al. (2007b) found that, when making risky decisions, inconsistent-handers reported being more influenced by the perceived risks of a behavior and consistent-handers reported being more influenced by the perceived benefits. Westfall et al. (2012) found that inconsistent-handers showed more inaction inertia and a greater sunk cost effect unless it was made clear that staying on a particular course would definitely result in a greater loss than abandoning it. Once it was clear that inaction would definitely result in a greater loss, there was a reversal with inconsistent-handers showing less inaction inertia. Finally, Bhattacharya et al. (2012) found that selectively activating the right hemisphere via Schiffer goggles increased the tendency for inconsistent-handers to focus on risks and consistent-handers to focus on benefits. It may be that these findings are related to a potential right hemisphere role in negative affect/withdrawal motivational states.

Handedness has also been used as a variable in traditional self-other/person perception paradigms. ICH seem to have an easier time taking other perspectives into account (Sontam et al., 2005; Lanning and Christman, 2010) and have better memory for counter-stereotypical information (Christman and Sterling, 2009). Additionally, sex and race effects on the Implicit Association Test (IAT) are modulated by handedness (Christman and

Sahu, 2012). For example, the weakest stereotyping was exhibited by ICH European Americans and by CH African-American males.

We will wrap up the present review with several additional findings that are not yet part of any broad research program, but which may prove to be promising leads in the future. While investigating possible associations between handedness and sleep architecture, Propper et al. (2004) found that ICH had shorter sleep latency and spent more time in NREM, although Propper et al. (2007) also obtained evidence that *consistent*-left-handers spend more time in NREM and less time in REM than *consistent*-right-handers, thus raising the possibility that *both* strength and direction of handedness should be considered when researching sleep. Christman (1993) discovered a compelling example of how degree of handedness may be related to preferences for certain motor tasks when he surveyed musicians and found that ICH were more likely to play instruments that require temporally integrated bimanual motor actions.

In conclusion, the studies reviewed above demonstrate a robust and systematic effect of degree of handedness in two well defined domains; episodic memory retrieval and belief updating/cognitive flexibility, and in other areas as well, including emotion and sleep architecture. It is hoped that this review will inspire a wider body of psychology investigators to incorporate this long neglected and misunderstood dimension of human individual difference into their research.

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Differences between left- and right-handers in approach/avoidance motivation: influence of consistency of handedness measures

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Hand preference is often viewed as a troublesome variable in psychological research, with left-handers routinely excluded from studies. Contrary to this, a body of evidence has shown hand preference to be a useful variable when examining human behavior. A recent review argues that the most effective way of using handedness as a variable, is a comparison between individuals who use their dominant hand for virtually all manual activities (consistent handers) versus those who use their other hand for at least one activity (inconsistent handers). The authors contend that researchers should only focus on degree of handedness rather than direction of preference (left versus right). However, we argue that the field suffers from a number of methodological and empirical issues. These include a lack of consensus in choice of cut-off point to divide consistent and inconsistent categories and importantly a paucity of data from left-handers. Consequentially, researchers predominantly compare inconsistent versus consistent right-handers, largely linked to memory, cognition and language. Other research on response style and personality measures shows robust direction of handedness effects. The present study examines both strength and direction of handedness on self-reported behavioral inhibition system (BIS) and behavioral activation system (BAS) scores, using evidence from a large (N = 689) dataset including more than 200 left-handers. There were degree of handedness effects on BIS and BAS-Fun Seeking, but effects are largely driven by differences between consistent left-handers and other groups. Choice of cut-off point substantively influenced results, and suggests that unless a suitable sample of left-handers is included, researchers clarify that their degree of handedness effects are applicable only to right-handers. We concur that strength of hand preference is an important variable but caution that differences related to consistency may not be identical in right and left-handers.

Keywords: EHI, consistency, BIS/BAS, left-handed, inhibition, handedness strength, handedness direction

INTRODUCTION

Hand preference has long been viewed as a troublesome variable in much research in psychology; left-handers in particular have been perceived as a noisy and unpredictable population and have often been excluded from studies (e.g., Ferrucci et al., 2013). However, a growing body of evidence suggests that handedness may provide some useful insights into individual differences in behavior (e.g., Wright et al., 2004; Kaploun and Abeare, 2010). Early research tended to examine *differences* between left- and right-handers and often found contradictory influences on behavior, although more recently there has been a move toward examining how handedness categories may influence the relationship with other variables (Beratis et al., 2011; Wright and Hardie, 2012; Hardie and Wright, 2013). In parallel, there is a growing body of research which focuses on strength of handedness, that is, the extent to which individuals favor their chosen hand (regardless of direction of preference). As a consequence, there has been debate in the literature about which of these aspects of handedness researchers should focus upon. The debate has been brought into focus by a recent review. This work contends that the most appropriate way to view handedness is using comparisons between consistent/strong handers who use their chosen hand for virtually all manual activities and inconsistent/mixed handers, who use their other hand for at least one activity (Prichard et al., 2013). Prichard et al. (2013) clearly advocate that "Instead of direction of hand preference being the variable of interest, it should be degree" (p. 1).

While Prichard et al. (2013) provide a very useful synthesis of strength of handedness research and expand our understanding of handedness (especially in the areas of memory retrieval and belief updating/cognitive flexibility); there are problems with the notion that direction is not an appropriate measure. For example, on the basis of an item response theory evaluation of one of the major handedness questionnaires (Oldfield's, 1971; Edinburgh Handedness Inventory, EHI), Büsch et al. (2010) strongly argue that only two classes of response emerge – left- and right-handed. Other researchers have argued that the most appropriate way to measure handedness is to examine a tripartite model – covering consistent-left, consistent-right and mixed-handers, based on factor-analysis (Peters and Murphy, 1992), neuroimaging (e.g., Knecht et al., 2000; Kirveskari et al., 2006) and behavioral studies

(Kaploun and Abeare, 2010). Finally, recent work in this area combines both direction and degree; Lyle et al. (2012a) found differences between consistency groups within handedness categories. This is potentially the most effective way of understanding the influence of handedness on behavior, and may be seen as a "gold standard" for future work, but such studies remain rare.

In order for degree of handedness to be considered as a valid variable, there is a need to examine the empirical and conceptual basis for this measure. After conducting a review of the methodology and theoretical stance of the authors of more than 30 articles using consistency of handedness as a variable, four major issues were identified. The first two are issues which are important for the field to debate and come to a consensus over, and are noted here simply in order to stimulate debate, while the second two issues will be empirically examined.

Firstly, the use of the EHI as a measure of handedness may be criticized. Oldfield's, (1971) EHI is a self-report measure and respondents answer questions regarding their preference to use a chosen hand "always" "mostly" or to use "either" hand on 10 manual tasks (e.g., writing, throwing). Scores are converted into a Laterality Quotient ranging from −100 (complete left-hand preference) through 0 (no preference) to +100 (complete right-hand preference). This instrument has been extensively evaluated since its' inception (Bryden, 1977; Williams, 1986; Dragovic, 2004), highlighting problems with the original scoring system (Fazio et al., 2012) which can lead to errors, as well as issues with the structure of the questionnaire itself (Dragovic, 2004). Recently, Milenkovic and Dragovic (2013) proposed that a seven-item version was superior to the original 10-item version, although Veale (2014) disputes this, instead offering her own four-item version. The crux of this debate is that some items may cause considerable measurement error, and that the 10-item version may lead to an overestimation of the proportion of mixed-handers (Dragovic et al., 2008; Büsch et al., 2010). The field needs to address these problems and agree on a standardized way to measure hand preference strength, before an accurate assessment of findings can be made.

Secondly, the use of a split to divide a potentially continuous variable (in this case, strength of handedness) into discrete categories has been criticized for at least the last 30 years (Cohen, 1983; Streiner, 2002; Irwin and McClelland, 2003). MacCallum et al. (2002), for example, argue that it can result in a loss of analytical power or may create falsely significant results. DeCoster et al. (2009) specifically examined the use of dichotomization of samples in psychological research, contacting a number of researchers to establish their rationale for this. The researchers followed this up with Monte Carlo simulations and conclude that continuous variables outperformed dichotomized versions in the majority, but not all of the cases. They produced criteria for dichotomising samples, but it should be noted that the emphasis was on the use of data to support the categorization process. This poses a question for researchers, if dichotomization is being used, should it be done on a seemingly artificial basis (median of hand strength), or should it rely on a split based on underlying latent classes (such as left versus right – Büsch et al., 2010)? Another option might be to use the mean score in each sample and convert the preference scores into stanines, and use stanine-5 exclusion to split the sample. This type of split is used in some areas of psychology (e.g., Moritz et al., 2006) and may be worthy of examination. Alternatively, DeCoster et al. (2009) suggest that extreme group analysis (i.e., selectively recruiting participants from the extremes) is a viable strategy, so perhaps this might be a useful way of testing consistency? The use of a median split for dichotomization needs to be more strongly justified by researchers, perhaps using DeCoster et al. (2011) recommendations.

Assuming that handedness should be examined using a non-continuous categorization, the third issue relates to the choice of the cut-off point to divide populations into consistent versus inconsistent handers (IH). The majority of studies use a notional median value of 80 on the EHI to split their groups into consistent and inconsistent (e.g., Christman and Butler, 2011; Lyle and Orsborn, 2011; Dollfus et al., 2012; Westfall et al., 2012), but it is not clear whether this median value is consistently found within individual samples. It is not common practice in many of these studies to publish their own median values, making the validity of a median split at 80 questionable. Even if the median value is established, there are additional problems with a lack of consistency in how to operationalize the split itself. For example, there are times when the consistency group is defined as scoring above the proposed median, i.e., 85 or above (Propper et al., 2005; Christman et al., 2009; Jasper et al., 2009). There are other times when it is defined as scoring at the median and above, i.e., 80 or above (Christman et al., 2006; Lyle and Grillo, 2014), or occasionally at some other figure such as 95 or above (e.g., Lyle et al., 2008). This lack of consistency across studies makes it difficult to directly compare findings and also suggests that *choice of cut-off* may influence results.

The final, and arguably the most important issue relates to how left-handers fit into this area of research. As a group, left-handers present a challenge to researchers, as they are generally less strongly lateralized than right-handers (Oldfield, 1971) and are relatively scarce, comprising approximately 10% of the general population (Ellis et al., 1988). Even more problematic, is that consistent or strongly lateralized (EHI < -80) left-handers make up only 2–3% of all individuals (Prichard et al., 2013). This makes them an extremely difficult group of participants to recruit, and only a few of the many studies of degree of handedness have been able to recruit a sufficient number of strong left-handers to be able to examine them as a group. As noted by Prichard et al. (2013) this means that the vast majority of this research predominantly compares inconsistent versus consistent groups largely, or exclusively, made up of right-handers (for an exception, see Lyle et al., 2012b). This conflicts with much of the literature which states their findings in terms of consistent versus IH, without making the rightward bias clear in terms of the narrative used in title, introduction and discussion (e.g., Niebauer, 2004; Westfall et al., 2010; Rose and Nagel, 2012). By failing to have enough data on strong left-handers, researchers are not in a sufficiently robust position to be able to say whether they are definitely the same as, or different from, strong right-handers. To clarify this, it is suggested that the field states clearly when the comparison group is predominantly made

up of right-handers only (for an example of this approach, see Christman, 2013).

The current study seeks to examine the issues of cut-off point choice and a lack of empirical data from left-handers, in light of Prichard et al.'s (2013) review and their strong assertion that direction of handedness is a "more powerful and appropriate way to classify handedness than the traditional one based on direction (right versus left)" (p. 1). Arguably this assertion is premature, particularly due to a lack of data from consistent left (CL)-handers, and that the studies thus far suffer from a lack of agreement in terms of the cut-off points used to test consistency effects. Consequentially, there is one main research question that requires answering: does strength of handedness influence left- and right-handers in the same way?

In order to do this, the present research examines the influence that strength of handedness has on a dataset which has a relatively large ($N = 202$) number of left-handers, seeking to understand the potential relationship both strength and direction may have on findings. As noted previously, recent work on degree of handedness has been extensively linked to areas of cognition such as memory. The present study extends this into an area of personality, focusing on the relationship between handedness and motivation measured by the behavioral inhibition system (BIS) and behavioral activation system (BAS) scales of Carver and White (1994). The BIS/BAS scales are a self-report measure of the revised reinforcement sensitivity theory of personality (rRST; Gray and McNaughton, 2000). Briefly, this theory postulates that behavior is broadly influenced by three interacting systems; the BAS which motivates approach, reward and impulsivity; the fight-flight-freeze system (FFFS) which relates to fear of a negative outcome, punishment and withdrawal; and the BIS which resolves conflict within or between the other two systems (see Corr and McNaughton, 2008 for details). Prior studies have linked the right-hemisphere to behavioral inhibition and behavioral avoidance (e.g., Davidson, 1985, 1995, 1998), with Sutton and Davidson (1997) describing the left hemisphere as corresponding to approach behavior and the right hemisphere to avoidance behavior. For example, Shackman et al. (2009) have shown that individuals reporting themselves as behaviorally inhibited have an increased resting activity within their right dorsolateral prefrontal cortex. Other work links the right-hemisphere to infants' temperamental shyness, anxiety, and behavioral inhibition (Schmidt et al., 1999; Fox et al., 2001). Added to this are animal studies linking left-hand preference to delays in exploratory and investigative behavior (Hopkins and Bennett, 1994; Cameron and Rogers, 1999). There is evidence to suggest that measurements of lateral preferences are indicators of hemispheric preferences (Kinsbourne, 1997; Jackson, 2008), with the lateral preference indicative of a preference for the contralateral hemisphere. Previous work in this area (Wright et al., 2009) found hand direction differences, but the evidence has yet to be examined in terms of strength of handedness.

The current study seeks to investigate whether strength of handedness influences left- and right-handers in the same way, in terms of their relationship to BIS/BAS variables. This will be investigated empirically in two ways:

(1) Systematically examining the influence of cut-off points on strength of handedness findings. This will be done by comparing the dataset using a range of cut-off points derived from both the literature and the data itself.
(2) Examining how strength of handedness relates to other variables? This will use regression to examine whether the relationship between variables is the same for both handedness groups.

MATERIALS AND METHODS

PARTICIPANTS

Six hundred and eighty-nine participants took part in this study, 272 were male and 417 were female. The majority ($N = 502$) were in the 18–29 year category, comprising 76% of males and 71% of females. Two hundred and two were left-handed, 481 were right-handed, and the remaining six had no overall preference.

MEASURES

Demographics including gender and age category (18–29, 30–39, 40–49, 50–59, 60–69, and 70 + years) were collected. The EHI (Oldfield, 1971) was used to measure strength and direction of handedness, where participants were asked to indicate which hand they would normally use in each of ten tasks. Choices were Left Always, Left Mostly, Either, Right Mostly, Right Always, and as in previous work (Hardie and Wright, 2013) these were scored as −10, −5, 0, 5, and 10, respectively. Totaling this up yielded a score ranging from −100 (completely left-handed) to +100 (completely right-handed).

Carver and White's (1994) BIS/BAS scale was used to measure self-reported BIS, BAS and FFFS scores. This instrument has 20 items sub-divided into four categories. Three scales measure BAS – Reward Responsiveness (e.g., "It would excite me to win a contest"), Fun Seeking (e.g., "I often act on the spur of the moment") and Drive (e.g., "I go out of my way to get things I want". Originally only a single category measured BIS sensitivity (e.g., "Criticism, or scolding hurts me quite a bit") but this has subsequently been subdivided into FFFS (questions 2 and 22) and BIS scales (remaining five BIS questions) based on previous work (Corr and McNaughton, 2008; Hardie and Wright, 2013). In all cases, questions were answered as one of four options, ranging from "Very false for me" to "Very true for me" and scored as per Carver and White (1994).

PROCEDURE

Participants were recruited from both university and the general public through a sustained campaign of emails, website notices, recruitment at public science centers, and at science fairs over the course of around 12 months. We paid particular attention to the recruitment of left-handers, asking for people who considered themselves to be "left-handed" but we also recruited people more generally and tested all individuals who agreed to participate regardless of hand preference. Testing was carried out via a web-based presentation of the questionnaires, in a randomized order, after participants agreed to participate. The research was approved by the school research ethics committee and abided by the British Psychological Society Code of Human Research Ethics.

Table 1 | Distribution of EHI scores.

	Whole DATA set (*N* = 689)	Absolute strength (*N* = 689)	Left-handers only (*N* = 202)*	Right-handers only (*N* = 481)*
EHI score median	60	70	−65	75
EHI score mean (SD)	32.43 (64.1)	67.0 (25.8)	−59.0 (25.5)	71.22 (24.1)

	Male (*N* = 272)	Female (*N* = 417)	Male (*N* = 272)	Female (*N* = 417)	Male Left (*N* = 86)	Female Left (*N* = 116)	Male Right (*N* = 186)	Female Right (*N* = 295)
EHI score median	60	60	70	70	−65	−65	75	75
EHI score mean (SD)	29.9 (65.5)	34.1 (63.2)	68.1 (23.0)	66.3 (27.4)	−60.5 (24.4)	−57.8 (26.3)	71.6 (21.5)	71.0 (25.6)

**Six individuals who had an EHI score of 0 were removed for the left versus right figures.*

STATISTICAL ANALYSIS

Statistical analyses were carried out using SPSS v21. α was set at 0.05. The strength of hand preference scores were initially examined in terms of median scores, compared by direction of hand preference and gender. This was followed by an investigation of the influence of categorization system on measures of BIS/BAS, with all participants being assigned into Consistent/Inconsistent categories based on six separate classification systems with different cut-off points on the EHI. As gender has been shown to influence BIS/BAS scores, it was also included as a factor in all analyses. For each classification scheme the following three analyses were carried out:

Consistent handedness versus inconsistent handedness regardless of direction [ANOVA 2 (Gender) × 2 (Consistency)].
Consistent left (CL, consistent right (CR), and inconsistent (IH) handers [ANOVA 2 (Gender) × 3 (Consistency)].
Consistent left (CL), inconsistent left (IL), consistent right (CR), and inconsistent right (IR) handers [ANOVA: 2 (Gender) × 4 (Consistency)].

This was undertaken on BIS, FFFS, BAS-Reward Responsiveness (BAS-RR), BAS-Fun Seeking (BAS-FS), BAS-Drive (BAS-D), as well as a combined BAS score. For the second and third analyses, *post hoc* tests with Bonferroni corrections were calculated where a main effect of consistency was found. Only significant results will be reported.

Handedness was also examined in terms of a regression model, undertaking the following regression analyses:

EHI scores to include directionality and absolute scores to assess general relationship to strength.
Left versus right (as has been used in other studies, such as Hardie and Wright, 2013) where the analyses look at each category separately.

As gender was related to most of these measures, stepwise multiple regressions were used to examine the relationship between handedness and BIS/BAS variables. For each of the analyses, step one was to regress the BIS/BAS measures on gender. In step two, the measures of hand strength were introduced. A significant increase in R^2 when comparing the first to second step would indicate that handedness accounts for variance in BIS/BAS measures over and above those related to gender. If EHI is a significant predictor, then direction of handedness is important, while if absolute is significant then strength is most important. Beta weights provide the basis for examining any relationships. The key data is R^2 change and individual beta weights for the variables of interest.

RESULTS

Table 1 shows that the cut-off for the entire sample is 60, for left-handers only, it is –65 and for right-handers only, it is 75.

Table 2 | Influence of split value used, in terms of number of participants in each category.

Median categorization system	Consistent left-handers	Inconsistent left-handers	Consistent right-handers	Inconsistent right-handers
EHI85 (Consistent ± 85)	38 (5.6%)	164	184 (26.9%)	297
EHI80 (Consistent ± 80)	53 (7.8%)	149	235 (34.4%)	246
EHI75 (Consistent ± 75)	66 (9.7%)	136	261 (38.2%)	220
EHI70* (Consistent ± 70)	87 (12.7%)	115	304 (44.5%)	177
EHI60** (Consistent ± 60)	119 (17.4%)	83	367 (53.7%)	114
EHI40 (Strong ± 45)	145 (21.2%)	57	395 (57.8%)	86

**Based on actual median calculated from absolute strength figures.*
***Based on actual median calculated from EHI strength figures.*

EXAMINATION OF THE INFLUENCE OF CATEGORIZATION SYSTEMS

Table 2 shows variation within handedness categories depending upon the classification system used. The percentage of the sample categorized as consistent left – ranged from 5.6% of the sample in the most stringent to 21.2% in the loosest classification, and for CR-handers, these ranged from 26.9% (stringent) to 57.8% (loosest).

For all variables (except total BAS) gender was a significant factor. Females were significantly higher on BIS, FFFS and BAS-RR, while males were significantly higher on BAS-D and BAS-FS. All are $F_{(1,685)} > 4.7$, with p values = 0.035 or lower. There were no interactions between gender and handedness categories. The remaining analyses, therefore, focus on the influence of categorization. There were no main effects using either the EHI60 or EHI40 classifications.

TWO CATEGORY SPLITS: CONSISTENT (CH) VERSUS INCONSISTENT (IH) HANDERS

Table 3 shows that CH had a significantly higher FFFS score only when using the EHI85 cut-off point [$F_{(1,685)} = 12.17$, $p = 0.001$].

Table 3 | The influence of median split point and handedness categorization system on significant consistency of handedness differences found on the BIS/BAS scales.

Scale	Finding*	EHI85 Split	EHI80 Split	EHI75 Split	EHI70 Split
Two categories					
FFFS	CH > IH	0.001			
BIS	CH > IH	0.006	0.035	0.011	
BAS-FS	IH > CH	0.009	0.029	0.020	
Three categories					
FFFS	CR > IH	0.002			
BIS	CL > IH	0.001	0.046	0.005	0.014
	CL > CR	0.018			
BAS-FS	IH > CL	0.005	0.011	0.007	
BAS-RR	CL > CR			0.037	0.009
	CL > IH				0.046
Four categories**					
FFFS	CR > IL	0.008			
	CR > IR	0.035			
BIS	CL > CR	0.036			
	CL > IL	0.010			
	CL > IR	0.001	ns	0.007	0.038
BAS-FS	IL > CL	0.019	0.028	0.017	
	IR > CL	0.013	0.037	0.031	
BAS-RR	CL > CR				0.019

CH, consistent handers; IH, inconsistent handers; CL, consistent left-handers; CR, consistent right-handers; IL, inconsistent left-handers; IR, inconsistent right-handers.

***Six individuals who had an EHI score of 0 could not be assigned a direction (left or right) and were removed from the four category analyses.*

Looking at BIS scores, CH had significantly higher values in the EHI85 [$F_{(1,685)} = 7.73$, $p = 0.006$], EHI80 [$F_{(1,685)} = 4.47$, $p = 0.035$], and EHI75 [$F_{(1,685)} = 6.49$, $p = 0.011$] classifications. IH had a significantly higher value of BAS-FS, and like the BIS scores, these were only significant in EHI85 [$F_{(1,685)} = 6.87$, $p = 0.009$], EHI80 [$F_{(1,685)} = 4.78$, $p = 0.029$], and EHI75 [$F_{(1,685)} = 5.46$, $p = 0.020$] classifications. There were no other significant effects.

THREE CATEGORY SPLITS: CONSISTENT RIGHT (CR), CONSISTENT LEFT (CL) AND INCONSISTENT (IH) HANDERS

There was a significant main effect of category on FFFS scores (EHI85), $F_{(2,683)} = 6.23$, $p = 0.002$. *Post hoc* analyses revealed that only CR was significantly higher than IH ($p = 0.002$). For BIS, there was an influence of category on differences from EHI85 through to EHI70, all $F_{(2,683)} > 3.34$, p values = 0.036 or lower. Further analyses showed that CL was significantly different from CR in only the EHI85 system, but differed from IH in all classifications. For BAS-FS, there were main category effects in EHI85, EHI80 and EHI75 – $F_{(2,683)} > 4.55$, with p values = 0.011 or lower. In all cases, only CL was significantly lower than IH. There was an additional main effect of categorization on BAS-RR, for both EHI75 [$F_{(2,683)} = 3.24$, $p = 0.040$] and EHI70 [$F_{(2,683)} = 4.44$, $p = 0.012$]. In both cases CL were significantly higher than IH, and in EHI70 CL were also significantly higher than CR.

FOUR CATEGORY SPLITS: CONSISTENT RIGHT (CR), CONSISTENT LEFT (CL), INCONSISTENT LEFT (IL) AND INCONSISTENT RIGHT (IR) HANDERS

Comparing fully across hand direction and consistency categories helps to clarify where differences are arising (**Table 3**). Again the FFFS main effect is linked to the EHI85 classification only, $F_{(3,675)} = 4.27$, $p = 0.005$ and *post hoc* analyses revealed CR were significantly higher scoring than both IL and IR. The consistent groups did not significantly differ. For BIS, there were significant main effects of classification system from EHI85 through to EHI70, all with $F_{(3,675)} > 2.66$, p values = 0.047 or lower. In all cases CL were significantly greater than IR, except for EHI80 ($p = 0.052$). For EHI85, CL were also significantly higher in BIS than CR and IL. There were also main effects of classification system on BAS-FS scores for EHI85, EHI80 and EHI75 categories [all $F_{(3,675)} > 3.13$, p values = 0.025 or lower]. In all three cases, CL were significantly lower than both IL and IR. Finally, for EHI70 there was also a difference in BAS-RR scores, $F_{(3,675)} = 3.07$, $p = 0.027$, where only the CL group had significantly higher scores than CR ($p = 0.019$).

RELATIONSHIP OF STRENGTH OF HAND PREFERENCE TO OTHER VARIABLES

As the previous analyses predominantly found differences in BIS and BAS-FS then the following analyses are limited to these.

STRENGTH OF HANDEDNESS

In step 1 (Gender) the model successfully predicted BIS [$F_{(1,688)} = 50.22$, $p < 0.0001$, $R^2 = 0.07$] and BAS-FS [$F_{(1,688)} = 8.24$, $p = 0.004$, $R^2 = 0.01$] and was also the case in step 2 (Gender and Handedness), for both BIS [$F_{(3,688)} = 19.85$,

$p < 0.0001$, $R^2 = 0.08$] and BAS-FS [$F_{(3,688)} = 4.11$, $p = 0.007$, $R^2 = 0.02$]. In the case of BIS, the introduction of handedness in Step 2 significantly improved the model, $F_{(2,685)} = 4.41$, $p = 0.012$, $\Delta R^2 = 0.012$. Both EHI [$\beta = -0.088$, $t(688) = -2.26$, $p = 0.024$] and absolute strength [$\beta = 0.101$, $t(688) = 2.59$, $p = 0.010$] were significant but weak predictors of BIS. In the case of BAS-FS, handedness failed to significantly improve the model, and absolute strength was not a significant predictor. In general, handedness only explained a very small amount of overall variance.

STRENGTH OF HANDEDNESS FOR EACH CATEGORY

The sample was divided into left- and right-handers in order to investigate the relationship between BIS-measures and handedness strength separately. In this case, only absolute strength is used, as for each handedness group this is effectively the same figure.

Right-handers (i.e., EHI scores > 0, N = 481)

Neither BIS nor BAS-FS were significantly correlated with absolute strength. The model successfully predicted BIS in both Step 1 [$F_{(1,480)} = 47.96$, $p < 0.0001$, $R^2 = 0.09$] and Step 2 [$F_{(2,480)} = 24.15$, $p < 0.0001$, $R^2 = 0.09$] but the introduction of strength of handedness in Step 2 did not significantly improve the model. The model failed to successfully predict BAS-FS.

Left-handers (i.e., EHI scores < 0, N = 202)

BIS significantly correlated with absolute hand strength $r(202) = 0.140$, $p = 0.024$, but BAS-FS did not. BIS was successfully predicted in both Step 1 [$F_{(1,201)} = 7.95$, $p = 0.005$, $R^2 = 0.04$] and Step 2 [$F_{(2,201)} = 6.44$, $p = 0.002$, $R^2 = 0.06$] and the introduction of strength of handedness in Step 2 significantly improved the model $F_{(1,199)} = 4.78$, $p = 0.030$, $\Delta R^2 = 0.023$, with strength of handedness a significant predictor of BIS [$\beta = 0.150$, $t(201) = 2.19$, $p = 0.030$]. BAS-FS was also successfully predicted in both Step 1 [$F_{(1,201)} = 5.32$, $p = 0.022$, $R^2 = 0.03$] and Step 2 [$F_{(2,201)} = 3.80$, $p = 0.024$, $R^2 = 0.04$] but introduction of handedness in Step 2 did not significantly improve the model.

DISCUSSION

The current study did not find a median hand preference score of 80, a value which has been used in most previous studies (e.g., Christman et al., 2008; Westfall et al., 2010; Lyle et al., 2012a). The present sample comprises a relatively large sample of left-handers added to a sample of more than 400 right-handers, which yielded a median strength of 60. By taking absolute score (strength regardless of direction) this increases, but even examining only right-handers there is a median of 75. This calls into question the robustness of using a fixed value cut-off point based on a notional median score, and also illustrates the potential confound that may arise when using an actual versus notional median value. Differences in scoring of the EHI may potentially be a factor, as the original scoring system is problematic (Fazio et al., 2012). However, most researchers in the field appear to use a system dividing strength into multiples of 5 ranging from –10 for left-always to +10 for right-always (e.g., Christman et al., 2008; Lyle et al., 2012a; Hardie and Wright, 2013), so it is unlikely that scoring differences greatly influenced the current results.

Examining the influence of strength and direction of handedness on measures of Carver and White's (1994) BIS/BAS scales demonstrated that consistency of handedness had an influence on several measures. These were mainly related to BIS and BAS-FS which were significantly different across three different split points (EHI85, EHI80, and EHI75), suggesting that these were robust differences. As mentioned above, the current study did not find a median score of 80, so the use of this as a cut-off point may be questioned. When using a notional median of 80, which a majority of studies do (e.g., Jasper et al., 2008; Christman and Butler, 2011; Lyle and Orsborn, 2011; Westfall et al., 2012), the present study demonstrated some strong differences between CH and IH especially when using an "above median" cut-off of 85 (e.g., Propper et al., 2005; Jasper et al., 2009). For BIS scores, using the three category model (CR, CL, and IR) then CL were higher in BIS than the other two groups, suggesting that this group were strongly influencing the findings. In the four category classification (additionally splitting IH into IL and IR), CL were again significantly higher in BIS than the other three categories. Therefore, by selectively choosing this cut-off point to determine consistent handers, the current research findings could be interpreted as strongly arguing that consistent left-handers were significantly higher in BIS than other handedness groups and suggests that the increased behavioral inhibition of left-handers (e.g., Wright et al., 2009) may be driven by this group. This illustrates that when examined in a sufficient number, consistent left- and right-handers may differ from each other, supporting the contention that in the absence of enough data on left-handers other studies should not automatically assume similarity in behavior.

As expected, it was clear that the choice of cut-off point influenced the extent to which consistency effects on BIS/BAS were shown. This is an important finding, as comparing across other handedness consistency research there is a range of cut-off values for defining the "consistent hander" group, mainly equivalent to EHI85, EHI80, and EHI75 classifications used here. The present work is the first demonstration of the direct effect of choice of how to operationalize the median split point within the same dataset, highlighting the influence and also the need for consensus. A wider examination of the use of median splits across psychology yields a similarly mixed picture. A large proportion of them are largely silent in terms of how a median split is operationalized, for example, indicating that the variable in question was split into two groups based on the median, but not stating what was done with those at the median (e.g., Rydstedt et al., 2008; Tops and Bokshem, 2011; McCullough et al., 2012; Smith et al., 2013). It is common practice to have the split at a point scoring above the median (St Clair-Thomson and Sykes, 2010), and only a few studies indicate what is done with those falling at the median, usually adding them to the "low" group (e.g., Whaley, 2003; Hochwälder, 2009). If the field were to follow this convention, and assuming that the median of 80 can be justified, then this would equate to a consistency cut-off point of >80 on the EHI. As most handedness researchers use the EHI in a Likert scale format, this would equate to using the EHI85 system from the present study and it is suggested that this may be an appropriate way to create strength of preference categories.

Examining direction of handedness influences, only a handful of studies have had a sufficiently large sample of consistent left-handers in order to carry out the "gold standard" analysis of comparing all four groups (Lyle et al., 2012a,b; current study). Unfortunately, this means that for the majority of the literature, the position of consistent left-handers is somewhat confused. In some cases they are dropped from analysis as there is "evidence that strong left- and strong right-handers differ from one another. . ." (Christman and Butler, 2011, p. 18), or that "strongly left-handed differ from both the strongly right- and the mixed-handed, and thus may constitute their own group" (Propper et al., 2005, p. 754). In other cases they are subsumed because "strong left-handers resemble strong right-handers, with mixed-handers being distinct from the other two strongly handed groups" (Christman et al., 2009, p. 1184). This ambiguity is clearly demonstrated in Prichard et al.'s (2013, p. 3) comprehensive review, where they argue that researchers should not consider direction, while paradoxically acknowledging that most of the studies in their review "compared ICH with CR-handers." Arguably, the clearest position to take is to conduct the "gold standard" test if at all possible, but should there not be enough left-handers to test for this, to clearly state that the difference is based on mainly CR-handers.

In terms of the handedness related differences it appears that both strength and direction of handedness may both relate to BIS/BAS. A relationship between left-handedness and behavioral inhibition has become quite well established, through behavioral studies (Wright et al., 2004, 2013; Wright and Hardie, 2011), self-reported measures (Wright et al., 2009; Lyle et al., 2012a; Hardie and Wright, 2013), comparative evidence (Cameron and Rogers, 1999; Rogers, 2009) and models of hemispheric specialization linking the left-hemisphere to avoidance and the right-hemisphere to approach (see Rutherford and Lindell, 2011 for a review). Previous research found that consistent handers showed significantly higher behavioral inhibition than IH, which might be expected (e.g., Niebauer, 2004; Lyle et al., 2012a). When the present study examined the findings in terms of a relationship to direction of handedness as well (using EHI85) it clearly demonstrated that high scoring CL-handers have the highest mean BIS scores; that for left-handers regression analysis showed hand-strength was a significantly positive but weak predictor of BIS, and unsurprisingly BIS and hand strength were significantly correlated. Taken together, these findings suggest that for left-handers their relationship with behavioral inhibition links to degree of handedness in a way that is different from right-handers.

BAS-FS differences were also found, although these were in the opposite direction, with IH scoring higher than consistent. This is not surprising, as there is a body of evidence suggesting that IH are less conservative (Lyle and Grillo, 2014), more gullible (Christman et al., 2008), more open to non-standard ideas (Barnett and Corballis, 2002; Christman, 2013) and generally more risk aversive (Christman et al., 2007). Similar to the BIS findings, the main differences were largely driven by the influence of CL-handers being significantly different from all IH, but in this case, not CR-handers. This meant that regression analysis did not significantly differ between right- and left-handed groups. High BAS-FS has been linked to instant gratification and lack of future contemplation (Heym and Lawrence, 2010) and trait impulsivity (Smillie et al., 2006), and fits with behavioral evidence that left-handers may show an initial response delay when confronted with novelty (Wright et al., 2013).

Putting this together, the current study shows that left-handers may be different in some aspects of personality, compared to right-handers. The extent to which this can be directly applied to other areas of personality is not currently clear, mainly due to the paucity of data on left-handers. Therefore, the present work will hopefully act as a catalyst for other researchers to collect data from a sufficient number of left-handers, so that future hand preference findings are driven by data, rather than assumptions. What can be generalized to other work is our overall finding that consistent left- and right-handers may not always behave in the same way. This is because it contrasts with other work which argues that direction is not important (Prichard et al., 2013), and potentially leaves a question as to how should the field proceed? The recent work of Lyle et al. (2012b) offers some insight here, as although they found consistent left- and right-handers did not differ in terms of memory accuracy, they did find that left-handers as a group were slower to make judgments about memory. In other work Propper et al. (2007) found that consistent left-handers had a different pattern of sleep compared to CR-handers, and Lyle et al. (2012a) found that CR-handers were more anxious than IH, but for left-handers consistency did not relate to anxiety. As anxiety is seen as an outward sign of BIS activity (Corr and McNaughton, 2008) then the finding of Lyle et al. (2012a) resonates with the current results, and they give the intriguing possibility that direction may be important for left-handers and that strength may be important for right-handers.

The current research also has direct implications for the main theory for how hand strength may influence behavior. This theory relies upon the notion of an increased access to the right-hemisphere for IH (compared to consistent handers), allowing them to better coordinate across both hemispheres, that is, having better interhemispheric interaction (Christman et al., 2004; Niebauer, 2004; Propper et al., 2005; Jasper et al., 2008). When taken from the viewpoint of right-handers these arguments are more or less the same, but by adding consistent left-handers to the equation then these become potentially separable issues.

Indeed, for left-handers the right-hemisphere access argument can also be questioned due to anatomical evidence. This suggests that there are structural asymmetries in the central sulcus, where the dorsolateral motor cortex of right-handers is larger in the left-hemisphere, while the opposite is found for left-handers (e.g., Amunts et al., 2000; Klöppel et al., 2010). Additionally, the contralateral motor control arrangement of the primary motor areas of the brain means that left-hand action is largely operationalized via the right-hemisphere (Grabowska et al., 2012), making *increased* right-hemisphere access arguments for mixed-handers untenable for left-handers. Also contrary to the "IH having an increased right-hemisphere access" model is work by Cherbuin and Brinkman (2006). Using Poffenberger's Paradigm, they found that for left-handers, increases in hand strength were related to increases in efficiency of interhemispheric interaction and as a group, strong left-handers had the highest accuracy (in letter-matching within and across visual

fields), while strong right-handers had the lowest. On the other hand, arguments relating degree of handedness to interhemispheric interaction may be important. For example, Potter and Graves (1988) argued that CR-handers had a poorer interhemispheric transfer performance during a line drawing task when compared with non-right-handers. Luders et al. (2010) showed a negative association between corpus callosum size and strength of handedness, regardless of direction of handedness. This largely supports the idea that strength of handedness may demonstrate something important about how the hemispheres interact.

However, taking a wider examination of evidence, then it becomes apparent that compared to right-handers, left-handers appear to be more heterogeneous in terms of hemispheric organization and specialization (see Hervé et al., 2013, for a recent review). The assumption of consistent left-handers being similar to strong right-handers in interhemispheric connectivity is certainly open to debate, for example, Westerhausen et al. (2004) examined the corpus callosum, and found that left-handers had a higher density of fibers, suggesting greater interhemispheric connectivity. Other recent evidence examining motor control in the primary motor cortex, found that left-handers responded differently from right-handers when transcranial magnetic stimulation (TMS) was applied to either the dominant or non-dominant side (van den Berg et al., 2011). Right-handers were more disrupted in the task when the non-dominant side was stimulated, but left-handers split into two distinct groups – one more disrupted by non-dominant side stimulation, the other by dominant side. A similar conclusion has recently been drawn by Lyle et al. (2012a, p. 13) who argue that "consistency-related effects on interhemispheric interaction may not be the same among left-handers as among right-handers." In their review, Hervé et al. (2013) make suggestions about future research questions, these include; investigating if left-handers as a group have a different neural organization than right-handers; do left-handers show variation in their intrinsic brain connectivity and how can structural and/or functional asymmetries be related to cognitive functioning in left-handers? Taken together, this suggests that the present theoretical underpinning of degree of handedness differences, while applicable to right-handers may need to be further investigated and/or re-evaluated when considering left-handers.

LIMITATIONS

The current study has some limitations, including the presentation of questionnaires using a web-based approach. By using this medium, there is the potential problem of participants not responding accurately or honestly. However, while this could occur within the dataset, there is no *a priori* reason to expect that the rate of error would differ according to handedness category, so the main findings should be robust. In addition, although web-based data was collected, the initial recruitment of participants was made before passing on the survey link, meaning that there was some degree of control of the process. It is therefore acknowledged that there will be an element of self-selection in terms of willingness to participate, but again there is no strong reason to believe that this would introduce a bias that would artificially create handedness based results. In order to improve accuracy from self-report questionnaires, future work should include either a pre-existing lie scale or add validity questions, to allow for removal of any clearly invalid responses (Fervaha and Remington, 2013). Finally, the regression results suggest that overall; strength of handedness is a very weak predictor of personality, while direction of handedness seems to demonstrate robust differences between left- and right-handers. This suggests the need for a much wider investigation of the validity of strength of handedness as a predictor.

CONCLUSION

The present study reinforces the view that consistent left- and right-handers do not always behave in the same way. The clear implication is that researchers need to gather sufficient data on consistent left-handers in order to delineate where behavior either converges with, or diverges from, right-handers. It also highlights the need for the handedness research community to be able to robustly defend the dichotomization of hand consistency on the basis of a strong theoretical and empirical evidence base, including an agreed split-point.

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Hand preference, performance abilities, and hand selection in children

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It is widely know that the pattern of human handedness is such that approximately 90% of the population is right handed with the remainder being left handed, at least in the adult population. What is less well understood is how handedness develops and at what age adult-like handedness patterns emerge. Quantified in terms of both preference and performance, a plethora of different behavioral assessments are currently in use with both children and adults. Handedness questionnaires are commonly used; however, these possess inherent limitations, considering their subjective nature. Hand performance measures have also been implemented; however, such tasks appear to measure different components of handedness. In addition to these traditional measures, handedness has been successfully assessed through observation of hand selection in reaching, which has proven to be a unique and effective manner in understanding the development of handedness in children. Research over the past several decades has demonstrated that young children display weak, inconsistent hand preference tendencies and are slower with both hands. Performance differences between the hands are larger for young children, and consistency improves with age. However, there remains some controversy surrounding the age at which hand preference and hand performance abilities can be considered fully developed. The following paper will provide a review of the literature pertaining to hand preference, performance abilities and hand selection in children in an attempt to ascertain the age at which adult-like patterns of hand preference and performance emerge.

Keywords: handedness, preference, performance, hand selection, reaching

Handedness is quite possibly the most studied human asymmetry; therefore much attention has been devoted to its assessment (e.g., Bryden, 1982; Steenhuis and Bryden, 1987, 1988, 1989). Control of the hands is contralateral, such that the right hand is under left hemisphere control and the left hand is under right hemisphere control (e.g., Annett, 1981a,b). This can be traced back to the work of Paul Broca, a nineteenth century neurologist, who hypothesized an association between neural control for language and an individual's hand preference. Clinical observations of language impairment caused by left hemisphere insult, in combination with the knowledge of his patient's right-handed preferences (Harris, 1993; Provins, 1997), led Broca to suggest that neural control for language mirrored an individual's hand preference.

In most cases, the left hemisphere is responsible for language function and manual preference (Sperry, 1974; Khedr et al., 2002; Vogel et al., 2003; Forrester et al., 2013). In particular, language is lateralized in the left hemisphere in 87–96% of the human population; however, not all people are right-handed (Annett, 1981a,b; Khedr et al., 2002), as one might assume. Although most right handers do fall within this distinction, as do 60–73% of left handers, right-hemisphere control for language or bilateral distribution across the two hemispheres can be observed in a small minority of individuals. This division has been confirmed through functional transcranial sonography, a non-invasive neural imaging technique that assesses the rate of cerebral blood flow during language tasks (Knecht et al., 2000a,b). Other researchers have demonstrated similar results using repetitive transcranial magnetic stimulation (rTMS; e.g., Khedr et al., 2002) and functional magnetic resonance imaging (fMRI; e.g., Pujol et al., 1999). The association between human hand preference and language function remains a topic of debate (Vauclair, 2004).

Considering the relationship between hand preference and language lateralization, it has been suggested that right hand dominance is a uniquely human trait (Annett, 2002; McManus, 2002). It is well known that 90% of the human population is right-handed, where this proportion has remained relatively consistent for approximately 5000 years (Coren and Porac, 1977). Handedness is typically described as the hand one prefers to use for unimanual tasks (Annett, 1970a). Two distinct components include *direction* and *degree*. Direction simply quantifies whether an individual is left- or right-handed. In comparison, degree identifies how strongly a person prefers one hand to the other (Steenhuis and Bryden, 1989). It is well-known that left handers generally display less functional asymmetry than right handers (e.g., Springer and Deutsch, 1998; Yahagi and Kasai, 1999), therefore the degree to which they use their preferred hand is significantly less in comparison to right handers.

Handedness is further divided into measures of *preference* and *performance*. Hand preference identifies the preferred hand for

completing a task, whereas performance differentiates between the abilities of the left and right hand on a particular task (McManus and Bryden, 1992). A relationship is commonly observed between these two constructs, such that performance abilities (i.e., skill) increases with the preferred hand (Annett, 1970b). But, this is not always the case (Jäncke et al., 1998). Research has revealed that right handers display more activation in the right hemisphere when using the left hand, than in the left hemisphere when using the right hand. It has been suggested that, in order for right handers to perform with their non-preferred, left hand, more effort is required (Jäncke et al., 1998).

Human hand preference emerges very early in an infant's life, where genetics and environmental influences are believed to play a key role in development. Some researchers have suggested hand preference in adulthood may be predicted from lateralized motor behavior in early gestation, comparing ultrasound observation of thumb sucking (Hepper et al., 1991), and neonate palmar grasp reflex strength (Tan and Tan, 1999). It has also been suggested that infant postural preferences can guide the development of handedness (Coryell and Michel, 1978; Michel, 1981), where observations of hand preference for reaching (Marschik et al., 2008) and grasping objects (Michel et al., 2002, 2006) have been observed to parallel hand-use distributions later in life. Research has indicated that hand preference can be reliably detected from 6-months onward (see Butterworth and Hopkins, 1993 for review of handedness in infants). Both cross-sectional (Gesell and Ames, 1947; Hawn and Harris, 1983; Peters, 1983; Michel et al., 1985; Cornwell et al., 1991; Morange and Bloch, 1996; Fagard, 1998) and longitudinal studies (Coryell and Michel, 1978; Ramsay et al., 1979; Carlson and Harris, 1985; Ramsay, 1985; Michel and Harkins, 1986; McCormick and Maurer, 1988; see Michel, 1984; Provins, 1992, for reviews) with infants indicate that some degree of hand preference is evident with the emergence of voluntary grasping. Together, these findings suggest that human hand preference may manifest itself very early in life. Nevertheless, variable hand use preferences (i.e., shifting from right to left hand use) have been noted in infancy, confirming that the development of hand preference during infancy is highly malleable (Corbetta et al., 2006) and different patterns of development exist (Michel et al., 2006).

Observing hand preference from early childhood to adolescence (i.e., ages 3–12) no general consensus exists surrounding the age at which adult-like handedness is actually attained. Some researchers (Archer et al., 1988; Longoni and Orsini, 1988; McManus et al., 1988) suggest that *direction* of hand preference is fixed at age 3, further explaining that degree increases between the ages of 3–7 and more gradually until the age of 9. Based on this idea, an individual's hand preference cannot be reliably assessed until 4 years of age (McManus, 2002). Other researchers have noted that children 3–4 years of age do not reliably select the preferred hand to perform unimanual tasks, and that it is not until the age of 6 that a clear preference can be observed (e.g., Bryden et al., 2000a). The equivocal findings here may be due to the different ways of quantifying hand preference and performance abilities in the research. Regardless, consensus has not yet been reached on the developmental milestones of handedness, and how adult-like patterns emerge. The following review will provide a synopsis of hand preference, performance abilities, and hand selection over the course of development, from early childhood to adulthood in an attempt to ascertain the age at which adult-like patterns of hand preference and unimanual skill emerge. More specifically, the first section will provide a review of traditional assessments hand preference (e.g., questionnaires), performance (e.g., pegboards, tapping tasks, etc) and performance-based measures of preference (i.e., observational assessments). The second section will explain non-traditional assessments of hand preference, paying particular attention to manual midline crossing and reaching into hemispace, as we argue that handedness assessed through the observation of hand selection in reaching provides some of the richest data regarding the development of hand preference and unimanual skill. The review will focus on development from early childhood (3-year-olds) to adolescence (12-years-old); however, some infant and adult literature will be included when necessary. As the majority of research is cross-sectional in nature, unless otherwise stated the review will primarily focus on cross-sectional data.

DEVELOPMENT OF HANDEDNESS: TRADITIONAL ASSESSMENTS

HAND PREFERENCE

Hand preference is typically assessed with a handedness questionnaire (McManus and Bryden, 1992). A plethora of instruments are currently in circulation, including the Crovitz–Zener Scale (Crovitz and Zener, 1962), the Annett Handedness Questionnaire (Annett, 1970a), the Edinburgh Handedness Inventory (Oldfield, 1971), the Lateral Dominance Examination (Reitan and Davidson, 1974), the Waterloo Handedness Questionnaire (WHQ; Steenhuis et al., 1990), and the Lateral Preference Inventory (Coren, 1993). Each of these questionnaires can be used to assess the direction of handedness (left- or right-handed). In addition, some enable the degree of handedness to be determined. Observing the current state of the literature, the Annett Handedness Questionnaire (Annett, 1970a), Edinburgh Handedness Inventory (Oldfield, 1971), and Waterloo Handedness Questionnaire (Steenhuis et al., 1990) are the most commonly used assessments. None of these questionnaires were explicitly designed for use with children; therefore, measuring handedness in children with questionnaires poses unique challenges, considering the inherent verbal requirements, and inability to assess children's familiarity of specific items and tasks. Nevertheless researchers have overcome these obstacles in a variety of ways. This includes parent or teacher report, oral administration, and/or asking children to perform each of the items, while the experimenter records responses. Use of questionnaires with children is prevalent in the literature.

In the largest survey study to date, Carrothers (1947) investigated the handedness of 225,000 school children (grades 1–12) in Michigan. The authors implemented a cross-sectional study design, observing a general tendency for left-handedness to decline with age. In order to deal with the limitations outlined previously, Carrothers (1947) relied on classroom teacher's report of their student's hand preference. In light of the fact that different teachers were assessing their own students, results must be interpreted with caution, due to bias from inter-rater reliability. Since Carrothers' (1947) study, numerous researchers have used

handedness questionnaires to assess developmental trends in hand preference. For example, Porac et al. (1980) assessed age-related changes in lateral preference (hand, eye, foot, and ear preference) in a large sample ($N = 1964$) of 8- to 100-year-olds using a 13-item behavioral-validated self-report battery. The authors did not indicate whether different procedures were implemented for younger participants. Within the battery, four questions were designed to quantify hand preference, where the remaining questions addressed foot, eye, and ear preference. Results indicated that the number of individuals classified as right-handed increases with age, where two developmental hypotheses were presented to explain findings. First, the authors noted environmental pressures toward right-handedness, highlighting that, prior to 1930, use of the left hand for writing was frowned upon (Blau, 1946). Nevertheless, their review of 34 studies from 1913 to 1976 indicated that social constraints account minimally for changes in hand preference (Porac et al., 1980). Left-handedness has become more culturally accepted in the western world; however, the number of left handers remains considerably lower in eastern cultures due to social constraints continuing to limit left-hand use (Ida and Bryden, 1996; Mandal, 1999). The authors also discuss developmental maturational processes, indicating that neural development continuing into the third decade of life (Yakovlev and Lecours, 1967) may influence the development of hand preference.

Some researchers have asked children to perform each action in order to observe the preference for an item listed on the questionnaire. Kilshaw and Annett (1983) observed hand selection to complete the 12-items of the Annett (1970a) Handedness Questionnaire These actions included: writing, throwing a ball, holding a tennis racket, striking a match, cutting with scissors, threading a needle, sweeping with a long-handles broom, shoveling with a long-handled shovel, dealing playing cards, hammering, using a toothbrush and unscrewing the lid of a jar. The distribution of hand preference did not change as a function of age; however, younger children were notably more variable in performance than older children. Brito and Santos-Morales (1999); Brito et al. (1992) also used this method to assess the hand preference of 4- to 7-year-old (Brito et al., 1992) and 8- to 15-year-old (Brito and Santos-Morales, 1999) Brazilian children using the Edinburgh Handedness Inventory. Based on questionnaire responses, children were divided into categories of hand preference adapted from Annett (1970b) by sex and age. The distribution of laterality quotients was *J*-shaped, where the frequency of left-handedness was greater in male children as compared to female children. This *J*-shaped distribution parallels distribution of hand preference observed in adults.

Others have opted to read questionnaire items out loud and have the experimenter record hand preference responses. This has proven successful for pre-school children as young as 2-years-old (e.g., Cavill and Bryden, 2003). Cavill and Bryden (2003) assessed handedness in 2- to 24-year-olds using the Revised WHQ (20-item). In comparison to Carrothers (1947), preference for the right hand was revealed across all age groups, where no differences among the age groups were revealed (Cavill and Bryden, 2003). These results parallel related reports in the literature (e.g., Hardyck et al., 1976; Kilshaw and Annett, 1983; Whittington and Richards, 1987; Bryden et al., 1991) which have also been unable to identify a significant change in the direction of hand preference as a function of age. That said, De Agostini et al. (1992) observed children below the age of 3 years demonstrate a significantly smaller right hand preference than noted in adults.

More recent investigations with the WHQ have revealed that most right handers score approximately the same on questionnaire items. Regardless of age, right handers typically report a right hand preference for items on the WHQ. In comparison, left-handed children display weaker hand preference tendencies at younger ages; therefore they do not display consistent hand preference tendencies over the course of development. Young left-handers (up to 8 year s of age) report they would use their left, right, or both hands equally for items on the WHQ. As left handers approach adulthood, the number of left hand responses increases; however, left handers, as a group are less consistent in hand preference tendencies than their right-handed counterparts (e.g., Bryden et al., 2000b; Cavill and Bryden, 2003).

Unfortunately, numerous problems exist with relying solely on self-report inventories of handedness. As mentioned previously, a number of handedness questionnaires are in circulation. As might be expected, the choice of questionnaire will undoubtedly influence results (Williams, 1991; Peters, 1998), as each possesses a unique type and number of items, and classification system. Different patterns of results can emerge solely on how handedness is classified (e.g., Peters, 1998; Steenhuis and Bryden, 1999; Bryden et al., 2005). Other concerns include researchers who select questionnaire items based on research needs (Brown et al., 2006). According to Peters (1998), researchers must "use different classification schemes, and examine how well these relate to the specific variables thought to relate to handedness and why" (p. 93). Finally, questionnaires are limited due to the inherent subjectivity, which makes administration to children and other special populations quite difficult, although clearly possible. Despite such problems a high degree of concordance between questionnaire items and observed preference in performance has been noted. Steenhuis and Bryden (1989) have observed that performance measures are related to preference items that assess the same activity, where Reib et al. (1998) have reported a 95.4% agreement. However, in young children ages 3- to 5-years of age, Bryden et al. (2007a) showed low correspondence between scores on a hand preference questionnaire and scores on an observational method of assessing hand preference (WatHand Cabinet Test described later), which includes similar items to the questionnaire. By age 6, a high degree of correspondence was found between these two measures ($r = 0.767$, $p < 0.01$).

Summarizing the research assessing hand preference in children, research using questionnaires have revealed that right handers typically report consistent right hand preferences from early childhood to adulthood. In comparison, left handers demonstrate weak hand preference tendencies that increase as a function of age, but rarely do left handers exhibit as strong preferred hand tendencies as their right-handed counterparts. It appears that direction of hand preference may be established at a relatively young age, as suggested by several researchers (Archer et al., 1988; Longoni and Orsini, 1988; McManus et al., 1988). However, it is clear that the degree or strength of hand preference requires

further refinement over the next several years. The establishment of a consistent and reliable degree of hand preference may be due to increased exposure to unimanual tasks, such as tool use and writing, over these years. In large part, the degree of hand preference may be a result of the amount of practice and experience a child has with certain motor skills.

HAND PERFORMANCE

In an attempt to eliminate confounding variables inherent to self-report measures (e.g., subjective nature, difficulty understanding questions, and response items), researchers have implemented performance measures. Such measures are easy to administer, require relatively few instructions, and are less open to the subjective interpretation of the participant. Measurement tools of this nature assess the differences between the two hands on a given task to identify which hand demonstrates superior performance, and to quantify the difference in performance between the two hands (Peters and Durding, 1979; Annett, 1985). Performance differences that emerge are thought to reflect the degree or strength of hand preference (Provins and Magliaro, 1993), where most tasks assess manual strength, speed, accuracy, and precision. Numerous performance measures exist, including hand dynamometers to assess grip strength (e.g., Whipple, 1914; Daniels and Backman, 1993; Häger-Ross and Rösblad, 2002), dot-filling tasks (Tapley–Bryden dot-marking task; Tapley and Bryden, 1985), finger tapping tasks (Peters, 1980), peg-moving tasks (Annett Pegboard; Annett, 1970b, and Grooved Pegboard; Matthews and Klove, 1964), and manual aiming tasks (Roy and Elliott, 1986), among others.

Early accounts of performance-based assessments of preference outline the use of hand dynamometer tests to assess strength differences between the two hands. For example, Whipple (1914), reporting on 6- to 18-year-olds stated that left hand strength averages 91–96% of right hand strength, observing that the strength of the preferred hand increases with age. Johnson (1925) examined 3- to 13-year-olds longitudinally with a dynamometer test. Over a year the percentage of left handers had decreased from 16 of 57 children to only one of 57 children. Daniels and Backman reported in their 1993 review that (1) grip strength increases with age; (2) male children are stronger than female children; and (3) right-handers are stronger with their preferred hand, whereas findings in left handers are inconsistent. More recent investigations (e.g., Häger-Ross and Rösblad, 2002; Molenaar et al., 2008; Koley and Melton, 2010) parallel these findings.

Hand performance has also been examined with dot-filling (Tapley and Bryden, 1985) and finger-tapping (Peters, 1980) tasks (Singh et al., 2001), where performance is also observed to improve as a function of age. Carlier et al. (1993) performed Tapley and Bryden's (1985) dot-filling task with left- and right-handed 7- to 15-year-olds. This task requires participants to place a dot in a circle following a pattern as quickly as possible. Dots are placed so each hand can work in its own region of hemispace. The preferred hand is used during the first and fourth trials, whereas the non-preferred hand is used in the second and third. Scores are averaged for both hands and a laterality quotient it computed to consider differences between preferred and non-preferred hand performance, and between left and right hand performance. Overall performance was similar for left and right handers, such that scores of both the preferred and non-preferred hand improved from the age of 7–14. That said, as a group, left handers were less lateralized than their right-handed counterparts. The degree of laterality was linked to age, where the direction of the effect was directly associated with the measurement. More specifically, when observing differences between the two hands, laterality increased with age (Carlier et al., 1993).

In a subsequent study, Carlier et al. (1993) compared children's performance on the dot-filling task with the finger-tapping test. Left- and right-handed 8- to 11-year-olds were instructed to tap a computer mouse with the index finger as quickly as possible from a "go" command until a "stop" command. Each trial time varied between 20 and 73 s. The dot-filling test was completed after the tapping test, either individually, or in the classroom as a group. As expected, older children performed faster and preferred hand scores were better than non-preferred hand scores. However, in comparison to Carlier et al. (1993) the difference between the two hands was not associated with age. The authors argued that the tapping task is not a complex skill that must be trained, whereas dot filling parallels writing skills, which is a learned trait. As such, results highlighted that task complexity plays a significant role in the size of the preferred-hand advantage. As such, the speed of dot-filling performance is better suited to differentiate the preferred hand, in comparison to variability of tapping.

Taking into consideration the assessment of manual speed, research has also focused on peg-moving tasks, such as the Annett Pegboard (Annett, 1970b) and the Grooved Pegboard (Lafayette Instruments, Model # 3205; Matthews and Klove, 1964) to assess age-related changes in performance. The Annett pegboard measures manual speed by timing the movement of 10 dowelling pegs from a row of holes (one inch apart) on one board to an identical board located parallel, eight-inches away from the starting board. Participants move each peg individually, using only one hand, and a laterality quotient can be calculated to identify performance differences between the hands. Observing concordance between preference and performance measures, the Annett pegboard has been shown to identify 86.8% of right handers and 80.8% of left handers, regardless of age, as determined via the WHQ (Bryden et al., 2007a). Annett's task may be better suited to assess age-related changes in performance, as it is easy to administer and seems to differentiate well between the hands. Similar to the Annett Pegboard, the Grooved Pegboard Test (Matthews and Klove, 1964) was designed to assess manual performance (Bryden et al., 2007a), however, the Grooved Pegboard requires a greater degree of manual precision to complete than the Annett pegboard. To complete this task, participants are traditionally asked to move 25 key-shaped pegs, individually, from a receptacle to an end position (place task). Modifications to standardized procedures, which require participants to remove the pegs and return to the receptacle (replace task), have been suggested to be a purer measure of motor speed (Bryden and Roy, 2005b) than the original placement task.

Literature surrounding the development of unimanual performance for peg-moving tasks indicates that peg-moving time decreases as a function of age (Kilshaw and Annett, 1983; Curt

et al., 1992; Singh et al., 2001; Annett, 2002; Dellatolas et al., 2003). In particular, Annett (2002) and Dellatolas et al. (2003) have noted an approximate 40% decrease in peg-moving time between the ages of 3 and 6, where variability in scores also decreased with age. Young children (3- to 6-year-olds) therefore perform significantly slower than older children and adults and with greater variability in their performance at 3-years-old in comparison to 6-years-old. This difference has been attributed to weaker lateralization evident in 3-year-olds which appears to strengthen with age. A longitudinal study (e.g., Fennell et al., 1983) provides support for this developmental aspect of hand preference. Reports of performance differences between the two hands also vary in the literature. Some studies indicate that asymmetry does not change as a function of age (e.g., Kilshaw and Annett, 1983; Annett, 2002; Curt et al., 1992; Dellatolas et al., 2003). As outlined by Annett, "differences are slightly larger in young than older children but this is a function of the rapid rates of growth in the early years" (p. 552). In comparison, others have noted significantly larger asymmetries for young children, in comparison to adults, who have the smallest performance differences between the hands. Likewise, the laterality quotient for children has been reported larger than what is observed for adults (Roy et al., 2003; Bryden and Roy, 2005a; Bryden et al., 2007a). Such effects have been found primarily for the Annett Pegboard.

With respect to measures of hand performance with the Grooved Pegboard, researchers have determined that, for young children, performance differences between the hands are further exaggerated in tasks that require skill and precision. These differences disappear in 10- to 12-year-olds, as children's performance becomes increasingly adult-like with age (Bryden and Roy, 2005a; Bryden et al., 2007a). With respect to adult performance, right handers have been observed to complete the task significantly faster with the right hand; however, performance differences between the hands are almost negligible, but still significant (Roy et al., 2003).

The inconsistent findings in the literature highlight that, despite the obvious benefits of utilizing performance measures (e.g., fast and easy to administer), such measures have inherent limitations. It appears that tasks requiring precision aiming result in larger performance differences between the hands than less complex tasks (Carlier et al., 1993; Bryden and Roy, 2005a; Bryden et al., 2007a). Thus, each unimanual task likely measures only one aspect of manual performance abilities (e.g., speed or accuracy); however, there are likely several factors underlying performance differences between the hands, as handedness is a multidimensional trait. Support for this suggestion comes from Corey et al. (2001), who measured hand preference of left- and right-handed adults using Briggs and Nebes' and Oldfield's handedness inventories, in conjunction with three of the aforementioned performance tasks (Grooved Pegboard, finger-tapping, and grip strength). Analysis revealed that use of one hand performance measure was not sufficient to classify an individual as left- or right-handed. However, using finger tapping and Grooved Pegboard scores together did enable correct classification of participants. Results of this study highlight that hand preference is a multidimensional trait; therefore, during assessment the numerous components of hand preference and performance must be considered (Corey et al., 2001).

Summarizing, research using performance measures to assess hand preference has revealed that skilled unimanual performance increases as a function of age from early childhood to adulthood, where 3- to 6-year-olds show more variable and slower movements than children older than 6 and adult-like performance emerging between 10- to 12-years of age. The pattern of results suggests that practice, learning and experience play a role in refining the performance of both the preferred and non-preferred hands. The size of performance differences between the hands is a topic of debate, as some researchers have identified notable differences in younger children that decrease with age; whereas others have noted similar patterns of lateralization over the course of development. Such differences may in part be due to the performance tasks used in the studies, where learned tasks that require high levels of precision result in significant effects of age on the performance differences between the hands. In contrast, tasks that are less complex and not necessarily learned, such as finger tapping, may not show age-related changes in the size of the preferred-hand advantage. It is clear that investigators must choose carefully which performance task to utilize in research investigating manual performance differences in children. With respect to variations among handedness groups, the literature has shown that right handers demonstrate a greater preferred-hand advantage, where left handers display similar performance with both the preferred and non-preferred hand, as both children and adults. The performance of left handers on various unimanual tasks indicates these individuals are less lateralized in general than their right-handed counterparts. Because both hands of left handers are relatively equivalent in performance abilities, it may take developmentally longer for left handers to determine which hand is actually more efficient at performing particular tasks, hence explaining their variable performance on hand preference questionnaires.

OBSERVATION OF HAND PREFERENCE

Given the problems of assessing hand preference in children using either hand preference questionnaires or performance tasks, Krombholz (1993, c.f., Kastner-Koller et al., 2007) therefore suggested measuring handedness through the use of video observations of children in their natural environment. Observational-based assessments of handedness have thus been implemented as an alternative measure of hand preference, where these measures are both appropriate and effective for use with children (e.g., Karapetsas and Vlachos, 1997).

Hardyck et al. (1975) assessed handedness in a very large sample ($N = 7688$) of students in grades one to six. Left handers comprised 9.6% of the sample, with 10.5% of male children ($n = 3960$) and 8.7% of female children ($n = 3728$) being left-handed. Three behavioral tasks included handwriting, paper cutting, and picking up a paper tube to look through it (paper tube used to assess eye preference). Results revealed consistent hand preference for all the tasks, with no association with age. Because mixed handedness was observed so infrequently, the authors argued "to render unnecessary the categorization of mixed-handed" (Hardyck et al., 1975, p. 371). In a similar study, Nachshon et al. (1983) assessed laterality (hand, eye, and foot) preferences in a large sample of 7-year-old children. To measure hand preference, three colored pencils were placed at the midline and the child was asked to make an "X"

on a piece of paper. If children used the same hand for all three pencils, the test was completed. If, however, children displayed inconsistent hand selection, the test was repeated twice more. A score less than four out of five was coded as variable. The authors observed greater than 80% of children were right-handed, where approximately 37% of children displayed consistent right and 3% displayed consistent left preference.

Similar to Hardyck et al. (1975) and Nachshon et al. (1983), Coren et al. (1981) examined a battery of lateral preference tests in a group of 3- to 5-year-old preschool children and high school students (i.e., young adults). These performance tests assessed hand, foot, eye and ear preference, where specific hand performance tests included: (1) picking up a ball and throwing it to the experimenter; (2) touching the nose with a finger; (3) picking up a crayon and drawing a circle; (4) picking up a small ball with a spoon; and (5) cutting out a piece of paper with scissors. Based on performance of all items, each child was classified according to right-side, mixed or left-side preference. Analyzing hand preference dichotomously both pre-school and high school students demonstrated a strong right hand preference; however, when separating participants based on strength of handedness, a difference in age emerged. High school students were significantly more right-handed, thus highlighting that consistency of right hand use increases as a function of age. Using the same battery of tests, results were replicated by Longoni and Orsini (1988) in a group of 4- to 6-year-old preschool children.

Rymar et al. (1984) also included a battery of performance items to assess developmental trends in hand preference. Six to 15-year-old elementary and junior high school students were observed performing various tasks: writing, throwing, using chopsticks, using scissors, drawing, hammering and using a spoon. Participants were classified according to left-, mixed-, or right-handed and data was analyzed according to age. Results highlighted fluctuating patterns of hand preference, such that students in the 6th grade of elementary school and 1st grade of junior high (11- to 13-year-olds) demonstrated the strongest hand preference. Similarly, Singh et al. (2001) observed the hand used to complete 10 simple tasks: writing, erasing, lighting a match, throwing a ball, hammering, using scissors, picking up small objects, brushing teeth, using knife, and combing hair. Hand preference responses were significantly different according to age, such that more 4- to 6-year-olds displayed weak hand preference tendencies in comparison to 7- to 11-year-olds. This shift from weak to strong hand preference was observed in both left- and right-handed children.

More recently, Kastner-Koller et al. (2007) integrated 48 tasks (i.e., 16 tasks administered three times) of visuo-motor skill and general development into a treasure hunt. Using Steenhuis and Bryden's (1989) ideas as a guide, movement components included (1) proximal movements, (2) distal movements, (3) grasping objects and (4) manipulating objects. Each component was performed in two stages: (1) precise skilled movements, and (2) fast, automatic movements. For example, precise proximal movements included throwing a ball and sweeping the floor, whereas an automatic proximal movement included pointing to a dot and waving. Pre-school and kindergarten children were observed completing the tasks by a trained examiner to assess hand preference, where use of a parent-report questionnaire and observations of hand preference for drawing enabled researchers to validate the task. Results of this investigation revealed that, in comparison to left-handed children, right handers were more lateralized in their direction of preference. That said, regardless of an overall left or right hand preference, children who demonstrated consistent preferred hand use had higher developmental scores (assessed with the Vienna Developmental Test; WET, Kastner-Koller and Deimann, 2002) than children who demonstrated hand-switching between tasks. Furthermore, right-handed and ambidextrous children were observed to have superior visuo-motor skills in comparison to their left-handed counterparts (Kastner-Koller et al., 2007).

Where Kastner-Koller et al. (2007) opted for a treasure hunt to assess handedness in children, the WatHand Cabinet Test (WHCT[1]; previously referred to as the WatHand Box Test in Bryden et al., 2000a) is the observational measure of choice in our laboratory. Composed of a small, vertically oriented, two compartment cabinet with a door covering the top compartment, participants are asked to complete a complete a series of unimanual and bimanual tasks. These tasks include:

> lifting the cabinet door a total of four times, using a toy hammer, placing rings on hooks, tossing a ball to a target, opening a lock with a key, using a screwdriver, pushing small buttons on a gadget, picking up a candy dispenser that was behind the cabinet door (Bryden et al., 2007b, p. 831).

Due to the number of tasks, several scores can be obtained from the WHCT, including a *skilled score*, a *consistency score*, a *bimanual score*, and finally, a *total score*. The *skilled score* is computed from seven tasks that require manual dexterity (use a toy hammer, place a washer on a hook, toss a ball to a target, open a lock with a key, use a screwdriver, push small buttons on a gadget, use a crayon). A laterality quotient $[(R - \mathrm{L})/(R + L) \times 100]$ is computed, taking into consideration the number of tasks completed with the left and right hands. The *consistency score* is computed by averaging right-hand performance of the four unimanual door lift tasks (scored 0, 1, 2, 3, or 4 out of 4; Bryden et al., 2007b). In comparison, the *bimanual score* records the hand used to open the cabinet door in relation to the hand used to retrieve the candy dispenser. A score of 1 represents opposite hand use for opening the cabinet and reaching for the object, and a score of 2 represents use of the same hand for both elements. Finally, a laterality quotient $[(R - L)/(R + L) \times 100]$ is used to calculate a *total score* from unimanual tasks (Bryden et al., 2000a, 2007b).

In order to assess the validity of the WHCT, Bryden et al. (2007b) completed the WHCT with 548, 3- to 24-year-olds (grouped 3- to 5-year-olds, 6-year-olds, 7-year-olds, 8-year-olds, 9-year-olds, 10-year-olds, 11-year-olds, 12- to 18-year-olds, and adults). Each participant also completed the Annett Pegboard and WHQ, to confirm hand preference, where both left and right handers were included in the study. Results revealed significant correlations between the WHQ ($r = 0.795$, $p < 0.01$) and the Annett Pegboard ($r = 0.542$, $p < 0.01$), therefore confirming the WHCT is a valid measure of hand preference to observe and

[1]For instructions on the WatHand Cabinet Test please contact Dr. Pamela J. Bryden (pbryden@wlu.ca, 519-884-1979 ext. 4213), Department of Kinesiology and Physical Education, Wilfrid Laurier University, 75 University Avenue West, Waterloo, Ontario, Canada, N2L 3C5.

quantify hand preference in individuals of all ages (Bryden et al., 2007b). Furthermore, the sub-scores of the WHCT provided a novel method of assessing different components of handedness in children. Notably, the skilled score assessed handedness similar to traditional assessments, which was likely due to overlap between tasks. It was thus suggested that the WHCT skilled score could be used individually to assess handedness (Bryden et al., 2007b).

The aforementioned assessments of handedness in typical development with the WHCT (Bryden et al., 2000b) has demonstrated that young children (3- to 4-year-olds) are the least lateralized and consistent in comparison to older children (6- to 7-year-olds and 9- to 10-year-olds) and adults. It has thus been proposed that young children (3- to 5-year-olds) display weak hand preference tendencies until the age of 6, where hand preference is established and continues to strengthen as a function of age. In comparison to their right-handed counterparts, left-handed children show depressed scores when investigating consistency of hand preference. Some left-handed children appear to use their non-preferred at least half of the time. It is generally understood that left-handed children demonstrate significantly greater non-preferred hand use in comparison to their right-handed counterparts, who, independent of age, appear to use their preferred hand almost exclusively (Bryden et al., 2000b). Overall, the WHCT has been documented as the most accurate means of assessing hand preference in children due to minimal verbal requirements involved in the observational-based assessment (Bryden et al., 2007b). As such, Bryden et al. (2007b) suggested that the WHCT would be an excellent tool for use with special populations. In fact, the WHCT has been successfully used to assess hand preference in children with Autism Spectrum Disorders (e.g., Markoulakis et al., 2012).

Summarizing then, observational assessments of hand preference have noted an increase in strength of hand preference with age. Such findings mirror those found using hand preference questionnaires noted earlier. In particular, young children, between the ages of 3- and 5-years-old, display weak, inconsistent hand preference tendencies. With age and maturation, hand preference becomes gradually more consistent, resulting in a shift from weak to stronger hand preference tendencies.

DEVELOPMENT OF HANDEDNESS: NON-TRADITIONAL ASSESSMENTS

MANUAL MIDLINE CROSSING

In addition to traditional measures, which quantify hand preference using preference, performance and observational assessments, researchers have also examined how hand preference influences hand selection in manual midline crossing. Manual midline crossing is observed when an individual reaches across the body midline into contralateral hemispace. To successfully execute such movement requires inhibition of the ipsilateral reach and, subsequent contralateral effort (Bishop, 1990). Failure to complete manual midline crossing has been well documented in the literature. For example, Head (1926) observed impairments first hand during the First World War, in which traumatized solders with aphasia were unable to complete contralateral movements. Researchers have since implemented manual midline crossing assessments to investigate developmental trends.

Gordon (1923) developed a measure of children's ability to cross the midline, observing an increase in ability with age. It is well understood that manual midline crossing is expected to emerge during infancy as a part of the typical progression of perceptual-motor development (Benton, 1959; Kephart, 1971). Bruner (1969) proposed the term "midline barrier" to describe infant's early difficulties with contralateral movements, where research to date has outlined a specific developmental sequence underlying manual midline crossing. Infants' initial reaches are primarily ipsilateral but progression to reaching for objects at the midline occurs quickly. Contralateral reaching begins to emerge between 18 and 20 weeks, reflecting the child's exploration of their environment (White et al., 1964; Ball and Edgar, 1967; Wapner and Cirillo, 1968; Kephart, 1971; Greenman and Legg, 1976; Provine and Westerman, 1979; Liederman, 1983). It has been suggested that this period represents a shift from extracallosal to callosal control of interhemispheric communication. In particular Liederman (1983) noted that maturation of the corpus callosum is a required prerequisite for development of hand preference and bimanual coordination. Others have described that manual midline crossing is necessary for developing a skilled preferred hand (Provine and Westerman, 1979; Ayres, 1972, 1980). Manual midline crossing is well established in various tests by the age of 2 (Stilwell, 1987); however, reaching into contralateral space is a skill that gradually improves with age. Various methods of postural compensation are observed, as young children avoid contralateral reaching during visuomotor tasks (Roach and Kephart, 1966). It has been suggested that failure to cross the midline by the age of 3–4 may highlight, at an early state, problems with perceptual-motor development that will manifest later in life (Michell and Wood, 1999).

Based on research in hemispatial neglect, line bisection tasks have been used to investigate age-related changes in manual midline crossing (Bradshaw et al., 1987; Bradshaw et al., 1988; Dellatolas et al., 1996; Van Vugt et al., 2000; Dobler et al., 2001; Hausmann et al., 2003). Young children avoid movements to contralateral space, using each hand in its own region of space and displaying patterns of "symmetrical neglect." This behavior is typically observed from 4-years-old to 7- or 8-years-old (Bradshaw et al., 1987, 1988; Dobler et al., 2001), at which point adult-like patterns begin to emerge. Adults typically display "pseudoneglect" (Bowers and Heilman, 1980), where a line is transected to the left of center. Hausmann et al. (2003) noted that the shift from immature to mature control persists through the ages of 10- to 12, where numerous researchers have indicated developmental changes may parallel the transition from childhood to adolescence and subsequent maturation of the corpus callosum (Finlayson and Reitan, 1976; Dodds, 1978; O'Leary, 1980; Pujol et al., 1999; Giedd et al., 1996).

In addition to line bisection tasks, researchers have also observed children's willingness to cross the midline to reach contralaterally. Developmental trends have been noted in a variety of age groups using several different tasks. Schofield (1976) observed the tendency for 3- to 8-year-old children to make preferred hand contralateral responses in Head's (1926) Hand, Eye and Ear Test. Children observed a female model touch her left or right ear or eye with the left or right hand and were asked to copy the

movement. The number of preferred hand ipsilateral and contralateral responses was recorded. Younger children used each hand in its own region of hemispace and showed few if any contralateral reaches with the preferred hand. A gradual increase in preferred hand reaches across the midline was noted with age. However, the authors highlighted the lack of a "straight-forward developmental trend" (p. 576), as 4-year-olds were observed to cross the midline as often as 7- and 8-year-olds, and 6-year-olds made fewer movements across the midline than any other age group. The authors summarized that, although children were more likely to use the preferred hand, this was not always the case. Non-preferred hand responses were apparent, but less likely than preferred hand reaches, especially when reaching across the midline.

Cermak et al. (1980), Cermak and Ayres (1984), Atwood and Cermak (1986) have used the Space Visualization Contralateral Use score (SVCU% = (number contralateral responses/total number contralateral + ipsilateral responses) × 100) of the Test of the Southern California Sensory Integration Tests to assess the percentage of contralateral preferred hand reaches to pick up a block. Cermak et al. (1980) observed that preferred hand reaches across the midline increased with age in left- and right-handed 4- to 9-year-olds. Nevertheless, because of the variability in each age group, no statistically significant differences emerged. As noted, skilled hand preference develops with age; therefore, it was likely that picking up a block did not possess the skill requirement to drive preferred hand selection. Cermak and Ayres (1984) questioned whether the SVCU score could be use to differentiate between typically developing children and those with learning disabilities. Guidelines discriminated between younger (5- to 7-year-olds) children, but no differences emerged at 8-years-old. In line with the current review, the authors suggested that assessing manual midline crossing in older children may require more stringent criteria. Atwood and Cermak (1986) thus investigated how block placement from the midline might influence developmental trends in contralateral reaching. Right-handed 5- and 7-year-olds completed the space visualization test, where blocks were placed 1.9, 7.62, and 15.24 cm apart. Results demonstrated that the distance between objects does play a significant role in manual midline crossing, as younger children displayed less contralateral reaches at far distances.

Expanding on the knowledge gained from Cermak et al. (1980), which showed the frequency of midline crossing to gradually increase between ages 4 and 9, Stilwell (1987) completed "The Test of Manual Crossing" with 2- to 6-year-old children. Manual midline crossing was assessed with a center-hinged pegboard (see Stilwell, 1987, p. 786 for illustration). Participants were asked to place a peg in a designated hole, where the hand used for peg manipulation was recorded. Similar to Cermak's group (Cermak et al., 1980; Cermak and Ayres, 1984; Atwood and Cermak, 1986), the percentage of reaches across the midline was observed to increase as a function of age, where the absence of contralateral responses was rare. As such, results demonstrated that by 2-years-old, manual midline crossing is very immature, but nevertheless well established. Interestingly, in contrast to Atwood and Cermak's (1986) findings, the number of contralateral responses increased with increasing distance from the midline (i.e., from 5.08 to 15.24 cm).

Similar pegboard apparatuses have been used to identify at which point individuals will make awkward unimanual movements with the preferred hand, and subsequently switch to the non-preferred hand to complete a task. Bryden et al. (1994) used a long pegboard (see Bryden et al., 1994 for illustration) and long dot-filling task. For the long pegboard task, two pegs (one small, one large) were placed in the first two holes (one small, one large) and participants were asked to "leapfrog" the pegs (i.e., large peg to next large hole to right, etc.) from one side of the pegboard to the other. Starting on the right side of the pegboard with the right-hand, participants were instructed to switch to their left hand when it felt appropriate to do so. The point at which participants switched hands was recorded. Similarly, with the long dot-filling task, a row of small circles was placed in front of participants, enabling participants to make a dot in each circle, starting with the right hand and switching to the left when comfortable. The point at which the participant switched hands was recorded. Using a laterality quotient to compute a magnitude of difference between the two hands, results successfully differentiated between left and right handers, where the long pegboard task proved to be a better assessment of handedness. Bryden et al. (1994) suggested the long pegboard provides a more objective assessment of handedness in comparison to a preference assessment. Furthermore, the authors stated the potential of such measure for use with young children and special populations; however, to date this has not been examined.

Where the aforementioned studies investigated manual midline crossing in the horizontal plane, researchers have also examined reaching throughout regions of hemispace. In 1996, Bishop, Ross, Daniels, and Bright developed the Quantification of Hand Preference task, which assesses hand preference in three task conditions (card pointing, reaching and posting) with a manual midline-crossing element. For example, in the card-reaching task Bishop et al. (1996) placed three playing cards at 30-degree intervals in hemispace (three positions in contralateral space, one at midline and three in ipsilateral space), each at a distance of 40 cm from the midline. Participants were asked to pick up a card and place it in a box at the midline, where the hand used to pick up the card was recorded. Bishop et al. (1996) suggested that this particular type of reaching paradigm is better suited for quantifying differences between handedness groups in comparison to other, more traditional assessments (i.e., questionnaires and pegboards). Displaying high homogeneity and test-retest reliability (Doyen and Carlier, 2002), this test has been shown to discriminate between hand preference groups based on direction and degree (Bishop et al., 1996; Calvert, 1998; Doyen and Carlier, 2002). Additionally, Bishop (2005) has stated that the card-reaching task is sensitive to developmental processes.

To assess performance on the card-reaching task from a developmental perspective, Carlier et al. (2006) completed the task with left- and right-handed children between the ages of 3 and 10. Adjustments were made to accommodate for children. For example, the number of cards retrieved per spatial position was doubled (i.e., originally 3, now 6) and an additional card was included so children did not realize they had reached for the last

card. Additionally, to facilitate non-readers, numbered cards were replaced with familiar pictures. Finally the distance between the midline and the card was shortened from 40 to 25 cm. Manual midline crossings were recorded, where, similar to early studies with manual midline crossing (e.g., Cermak et al., 1980; Stilwell, 1987) a developmental trend was observed based on number of crossings and spatial position. Statistically significant differences emerged between the youngest (3- to 4-year-olds) and oldest (8- to 10-year-olds) children. Furthermore, the contralateral hand was used less often to reach to extreme regions of hemispace. These results were replicated by Doyen et al. (2008) with 6- to 24-year-olds, demonstrating that adolescents and adults cross into contralateral space less often than 7- to 12-year-olds, regardless of sex or hand preference. The authors stated that these findings suggest the development of manual preference is an influential factor in the decision to reach into contralateral space. With age and acquired motor skill, task complexity decreases, enabling participants to reach into ipsilateral space with either the preferred or non-preferred hand. This argument is supported by research from individuals with a variety of neurodevelopmental disorders including Developmental Coordination Disorder, Specific Language Impairment (Hill and Bishop, 1998), Down syndrome (Groen et al., 2008), and Trisomy 21/Williams Beuren syndrome (Gérard-Desplanches et al., 2006).

As noted by Hill and Khanem (2009), the aforementioned studies, which assessed manual midline crossing with the Quantification of Hand Preference Task, were limited to the card-reaching task. All three components (pointing, reaching and posting) were thus completed with 4- to 11-year-old children (Hill and Khanem, 2009) to investigate how task constraints influence hand selection. As outlined previously, the reaching component required participants to pick up a specified card from hemispace and place it in a box at the midline. In comparison, the pointing task involved the least skill, requiring participants to point at a picture in hemispace; whereas, the posting task, which was the most challenging task, required participants to pick up a marble from the midline and post it into a cup with a small hole in its lid located in hemispace. Findings from other manual midline crossing tasks were replicated (e.g., Cermak et al., 1980; Stilwell, 1987; Carlier et al., 2006; Doyen et al., 2008). Task demands proved to influence hand preference when comparing reaching vs. posting and pointing vs. posting in contralateral space and at the midline. Distance from the midline also impacted the number of preferred hand reaches into contralateral space (Hill and Khanem, 2009). Younger children (ages 4–5) showed weaker hand preference being less likely to cross the midline in comparison to older children, and appeared to be more influenced by spatial position.

The previously discussed studies measured what has traditionally been defined as limb preference, in that if an individual prefers one hand, then that limb would be selected to complete a variety of unimanual tasks. But what drives the choice of one limb for such goal-directed movements? Gabbard and Rabb (2000) argued that several process underlie the decision to select one limb over the other for reaching, including (a) limb dominance, as related to hand preference, and (b) attentional or spatial information associated with the demands of the task. More specifically, in most tasks, hand selection is driven by hand preference. However, once the preferred hand is biomechanically constrained by the degrees of freedom required to accomplish the task, and therefore unable to perform with the most efficient and comfortable response, the non-preferred hand is selected. In more simple terms, this behavior can be explained by hand selection according to object proximity. This is referred to as the *kinesthetic hypothesis* (Gabbard and Rabb, 2000; Gabbard and Helbig, 2004). Mark et al. (1997) have also suggested that postural dynamics guide hand selection and choice of reach. More specifically, people perceive the comfort of performing a reach with a single (arm only) or multiple (use of upper torso) degrees of freedom; therefore use the non-preferred hand in contralateral hemispace to avoid a multiple degrees of freedom reach.

Another possible explanation is the *hemispheric bias hypothesis*, where each hand is used in its own region of hemispace, because performance (i.e., speed and accuracy) is greater in ipsilateral space (Bradshaw et al., 1990; Verfaellie and Heilman, 1990; Umilta and Nicoletti, 1992; Elliott et al., 1993; Hommel, 1993; Carnahan, 1998). To act in contralateral space requires interhemispheric communication, therefore results in decreased movement efficiency (e.g., Carson et al., 1992). Taking both hypotheses into consideration, it is suggested that hand selection may be initially driven by hand preference; however, information surrounding object location and task complexity may also be important (Bryden and Roy, 2006).

To assess reaching with respect to the kinesthetic and hemispheric bias hypotheses Gabbard and colleagues (Gabbard et al., 1998, 2001) used a reach-to-grasp task with a block presented in nine regions of hemispace. Left- and right-handed 5- to 7-year-olds and adults were initially blindfolded with the hands placed at a rest position. Participants were instructed to remove the blindfold, return the hand to the rest position and keep the eyes closed until the "ok" signal was given. At that point, participants were instructed to pick up the cube and place it in a box at the midline. As expected, preferred hand use was observed more frequently in ipsilateral space. However, in contralateral space, most participants used the non-preferred hand. Overall, hand preference was observed to drive movements at the midline and in ipsilateral space; however, in contralateral space, kinesthetic and hemispheric biases led to non-preferred hand responses. Right handers were more consistent in hand selection tendencies than left handers, which indicates that hand preference is a stronger controlling feature when programming reach-to-grasp movements.

In a related study, Leconte and Fagard (2006) had left- and right-handed 5- to 10-year-olds complete a task in which three identical objects (balls or dowels) were placed in left space, at the midline and in right space. Participants were instructed to grasp, grasp and relocate, or grasp the object and use it to pick up a sticker from the midline and relocate it. Results revealed greater preferred hand use in ipsilateral space and a shift to non-preferred hand use in contralateral space. Leconte and Fagard (2006) suggested that children "perceive the biomechanical constraints involved in the task and program the most efficient and comfortable response by using the hand closest to the object" (p. 91). The hemispheric bias hypothesis was also used to explain this behavior, such that use of the hand on the same side as the object was favored. Observing developmental trends, 5- to 6-year-olds used

each hand in its corresponding region of space. Manual midline crossing was observed to increase with age, as observed previously (e.g., Cermak et al., 1980; Stilwell, 1987), where 10- to 12-year-olds were most likely to reach across the body with the preferred hand. Age-related changes are likely due to variable hand preference tendencies in early childhood, which become increasingly more consistent with age.

To further delineate how individuals act in manual midline crossing, researchers have asked participants to manipulate the same object in varying contexts which alter the level of complexity. Bryden and Roy (2006; portions of study published in brief abstract/paper by Pryde et al., 2000) placed five toy objects at 45° in hemispace. Participants were asked to reach for an object in hemispace and complete a simple action (tossing the object) or a complex action (orienting and placing the object into a receptacle of the same size and shape). This enabled the researchers to examine the effect of task complexity, while recording the hand used to complete the task. Right-handed children (3- to 4-, 6- to 7-, and 9- to 10-year-olds) participated in this study, which observed use of the preferred hand through a greater range of hemispace than the non-preferred hand. Task complexity revealed no significant effects, which is likely due to the lack of sufficient degree of complexity. Similar to previous work, the authors noted a developmental trend in preferred hand use. Interestingly, 3- to 4-year-olds performed similar to adults, where preferred hand use decreased moving into left hemispace. In comparison, 6- to 10-year-old children used their preferred hand regardless of location in hemispace. This suggests that degree of hand preference in manual midline crossing is not consistent throughout development. The authors suggest that 3- to 4-year-olds use either hand at chance level, as they are exploring their environment. Children in the 6- to 10-year-old age range sacrifice cost-efficiency. Paralleling their stage of cognitive-motor development, they "tend to think in concrete, inflexible terms and are undergoing a period of motor skill refinement" (Pryde et al., 2000, p. 374). Finally, adults chose the most cost-effective movements, using their non-preferred hand in left space and preferred hand in right space (Bryden and Roy, 2006).

As observed in the previous studies, object location and task characteristics influence hand selection over the course of development. This has led researchers to question how reaching for a tool (i.e., an object which affords a specific action; Gibson, 1979) as opposed to an object, influences selection of the preferred hand. In adults, the preferred hand is typically selected to use a tool. However, this is not necessarily true when simply picking up a tool (Bryden et al., 2003; Mamolo et al., 2004). Observing this scope of research from a developmental perspective, a breadth of literature has examined traditional reach-to-grasp tasks involving tools in infancy (e.g., McCarty et al., 1999; Claxton et al., 2009). However, there exists a dearth of investigations involving children.

In a recent study Bryden et al. (2011) aimed to delineate how task complexity, object location and object type affects hand selection in children when considering a tool in comparison to an object with "no purpose" such as a dowel. Two hundred ninety-two right handers and 38 left handers (3- to 12- and 18- to 22-year-olds) were asked to pick-up and use one of five objects located in peripersonal space (five identical dowels and five tools: pencil, paintbrush, spoon, toothbrush, and a toy mallet or hammer), where the hand use to complete each element of the task was recorded. Results revealed that participants were more inclined to select their preferred hand when using a tool, as opposed to simply picking up the tool. Nevertheless, children did not differ in their hand selection for the different tasks when using the dowel, indicating the importance of tools and their saliency for action in hand selection. In line with previous findings (e.g., Calvert, 1998; Fagard, 1998; Gabbard and Helbig, 2004; Leconte and Fagard, 2006), children used their preferred hand most in ipsilateral space and at the midline, and tended to use their non-preferred hand in contralateral space. Furthermore, with age, the preferred hand was selected to a greater extent. Left-handed children showed an increased overall use of their preferred hand with age, whereas right-handed children used their preferred hand to the same extent across the ages. The only exception was 3- to 5-year-olds, who showed slightly depressed use of the preferred hand (Bryden et al., 2011).

Overall, the research on manual midline crossing and hand selection suggests a similar pattern of development of handedness as seen from the more traditional methods of assessment. Children aged 3- to 5-years-old explore the environment and objects surrounding them, using the hand that is closest to the task to be performed in most cases. While the direction of hand preference may be established at this age, the skill level of the two hands has not yet been well differentiated. This exploration of the environment may be key in the child learning which hand is more effective and skilled at particular tasks. Children between the ages of approximately 6 and 10 years have learnt through experience which hand is more efficient and thus select this hand overwhelming, even in situations where it is not biomechanically efficient to do so. Between the ages of 10 and 12 years, an adult-like pattern of handedness emerges for all measures of handedness, as children learn to be less reliant on their preferred hand and the skill level of the non-preferred hand increases. The manner in which handedness emerges strongly indicates that experience, learning, and practice are key components in refining handedness and in particular an individual's resulting degree of handedness.

SUMMARY AND CONCLUSIONS

Identifying the origins of human hand preference and mapping the developmental trajectory has been at the root of neuropsychological and psychological research for centuries (e.g., Marshall and Magoun, 1998). Several researchers have suggested that hand preference may be associated with sensory-motor experience (e.g., Coryell and Michel, 1978; Nudo et al., 1996; Provins, 1997; Corbetta and Thelen, 2002) or environmental factors (e.g., Harkins and Michel, 1988; Harkins and Uzgiris, 1991; Provins, 1997); however, the belief that hand preference is rooted in genetics (e.g., Levy and Nagylaki, 1972; Annett, 1985; McManus, 1985; Corballis et al., 2012) has prevailed for numerous decades.

The proportion of right and left handers in the human population has been described for approximately 5000 years (Coren and Porac, 1977). Annett (2002) and McManus (2002) have both stated that hand preference is a specifically human trait. Human hand preference appears to manifest itself very early in life (e.g., Corbetta et al., 2006; Michel et al., 2006) and run in families (Annett, 1972), which provides support for a genetic influence (e.g., Levy and Nagylaki, 1972; Annett, 1985; McManus, 1985;

see Corballis et al., 2012 for a review of genetic and evolutionary bases). In fact, data shows that there is a greater likelihood of a child with one left-handed parent becoming left-handed, in comparison to a child with two right-handed parents (Annett, 1972; McManus and Bryden, 1992; McKeever, 2000).

Although genetic accounts of hand preference seem plausible, they are limited in explaining individual development. For example, despite suggestions that hand preference emerges in infancy, variable hand-use strategies support the idea that hand preference is highly malleable (Corbetta et al., 2006) and different patterns of development exist (Michel et al., 2006). This variability is not limited to infancy. We have argued that there are three relatively distinct periods of refinement for handedness, and that experience, learning, and practice are key components at each of these stages. Young children (3- to 5-year-olds) typically demonstrate weak, inconsistent hand preference tendencies. This is particularly true for left-handed children. Young children are observed to use both hands to explore space. However, some object characteristics do influence hand selection. For example, hand selection preference is influenced when reaching to tools. Transitioning to older children in the 7- to 10-year-old range, there is an increase pattern of reliance on the preferred hand. Such strong, consistent hand preference ultimately drives performance differences between the two hands to increase, especially with respect to tasks requiring precision, as it is suggested the preferred hand is undergoing a period of motor skill refinement. Nonetheless, there is a relatively minute performance difference for speeded tasks. Children in this age range will select the preferred hand regardless of the task, object or position in space. This is thought to reflect children's stage of cognitive motor development.

Why are these variations in hand preference observed over the course of development? From a dynamic systems point of view, behavior emerges as one passes through life, "as the product of continuous intertwined reorganizations between multiple biological, environmental, and experiential factors that change and evolve as infants and children grow" (Corbetta et al., 2006). Handedness is thus sensitive to early sensorimotor experiences; however, after the foundation for basic motor skills is built, the motor system transitions to motor skill refinement (Corbetta and Thelen, 2002; Corbetta, 2005; Corbetta et al., 2006). This period of motor skill refinement is key to the development of handedness, and in particular the degree to which one prefers the dominant limb. Hand preference can be deemed adult-like when the reliance on the preferred hand drops (between the ages of 10 and 12 years), as performance differences between the two hands is small. This can be argued to be due to improvements in non-preferred hand performance due to additional experience and practice with manual skill.

While past research has successfully utilized both preference and performance measures with children and adults to examine hand preference, we would argue that handedness assessed through observation of hand selection in reaching provides some of the richest data regarding the origins of hand preference and unimanual skill. We also suggest that while direction of hand preference, at least right preference, is established relatively early in life (and likely determined genetically), the degree of hand preference and size of the performance difference between the hands requires significant exposure to a range of motor tasks, both complex and simple, involving tools and other objects, to develop fully. Clearly, hand preference has arisen from the interaction of object, task, environmental and individual characteristics, and thus these variables need to be taken into consideration when exploring hand preference.

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The influence of prior practice and handedness on the orthogonal Simon effect

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When stimuli are arranged vertically and responses horizontally, right-handed participants respond faster with right responses to stimuli presented above fixation and with left responses to stimuli presented below fixation, even when stimulus position is task-irrelevant (orthogonal Simon effect). The aim of the present work was twofold. First, we assessed whether the orthogonal Simon effect evident in right-handed participants is present also for left-handed participants (Experiment 1). Second, we investigated whether for both groups of participants the orthogonal Simon effect is influenced by the stimulus-response (S-R) mapping used for an orthogonal spatial S-R compatibility task performed 5 min before (Experiment 2). Our results showed that the orthogonal Simon effect significantly differed in the two groups, with left-handers showing an advantage for the up-left/down-right mapping (Experiment 1). Interestingly, the orthogonal Simon effect was strongly influenced by prior practice regardless of the participants' handedness (Experiment 2). These results suggest that the short-term S-R associations acquired during practice can override the long-term, hardwired associations established on the basis of handedness.

Keywords: orthogonal Simon effect, orthogonal spatial compatibility, handedness, practice paradigm, S-R associations

INTRODUCTION

It has been widely demonstrated that some stimulus-response (S-R) associations are easier to establish and faster to process than others. For instance, it has been shown that human performance is more efficient when stimuli and responses are ipsilateral, that is, on the same side (corresponding situations), than when they are contralateral (non-corresponding situations; e.g., Fitts and Seeger, 1953). The advantage for corresponding responses is evident even when stimulus location is irrelevant for performing the task and the response has to be emitted on the basis of a non-spatial stimulus feature (e.g., color or shape). For instance, when a right key has to be pressed in response to a red square and a left key has to be pressed in response to a green square, responses are faster if stimulus and response locations are on the same side as compared to when they are on different sides. The influence of the irrelevant spatial stimulus dimension on performance is known as Simon effect (Simon and Rudell, 1967; for a review see Proctor and Vu, 2006; Rubichi et al., 2006).

The Simon effect is considered an attentional phenomenon (e.g., Figliozzi et al., 2010) due to the interaction between two parallel and distinct processing routes, a slow conditional route and a fast unconditional route (e.g., Kornblum et al., 1990; De Jong et al., 1994), which are supposed to rely on different memory associations connecting stimuli and responses (Barber and O'Leary, 1997). When a stimulus appears, the slow conditional route activates the required response on the basis of task-defined associations connecting a stimulus to a specific response, while the fast unconditional route activates the response that spatially corresponds to the stimulus location through pre-existing stimulus–response associations, which are independent from instructions. When the two activated responses correspond, no competition arises. In contrast, when they are different, interference arises and the incorrect response needs to be aborted, affecting reaction times (RTs) and accuracy.

In the majority of the studies assessing spatial compatibility effects, both stimulus and response sets vary along the same dimension (see for example Rubichi et al., 2004, for a comparison between horizontal and vertical dimensions). However, these effects emerge even when "up" and "down" stimuli are mapped to left and right responses. This occurs both when stimulus location is relevant for task performance, a phenomenon known as orthogonal spatial compatibility (e.g., Weeks and Proctor, 1990; Lippa and Adam, 2001; Cho and Proctor, 2003; Proctor and Cho, 2006), and when it is irrelevant, a phenomenon known as orthogonal Simon effect (e.g., Cho and Proctor, 2005; Nishimura and Yokosawa, 2006; Cho et al., 2008). In both cases, even though there is not an evident spatial correspondence between stimuli and responses, performance is better when up stimuli are mapped to right responses and down stimuli are mapped to left responses (up-right/down-left mapping) than when up stimuli are mapped to left responses and down stimuli are mapped to right responses (up-left/down-right mapping).

To explain orthogonal correspondence effects, some authors proposed the so-called "asymmetric coding" account (e.g., Weeks and Proctor, 1990; Cho and Proctor, 2001, 2005) according to which stimulus and response alternatives with binary values are coded asymetrically as having a positive or a negative polarity. Specifically, "up" and "right" are coded as the polar referents for their relative dimensions (that is, up for the vertical dimension

and right for the horizontal dimension) and hence coded with a positive polarity, while "down" and "left" are coded relative to up and right and hence with a negative polarity (see also Clark and Chase, 1972; Olson and Laxar, 1973; Seymour, 1974). Hence, performance is better for the up–right/down–left mapping because there is correspondence between polarity codes of stimulus and response dimensions (that is, correspondence of positive polarity for the up–right mapping and of negative polarity for the down-left one). Polarity coding occurs for any dimension that has two extreme poles and the term polarity is an arbitrary label used to refer to the binary way in which the two extreme poles are coded.

The finding of an orthogonal Simon effect (Nishimura and Yokosawa, 2006; Cho et al., 2008) implies that the long-term associations between stimulus and response codes of the same polarity lead to automatic response activation (Bae et al., 2009). Interestingly, these S-R links do not seem to be as strong as those between a stimulus and the spatially corresponding response. Indeed, when the parallel Simon task is performed after practicing a spatial compatibility task with an incompatible mapping between stimulus and response, the Simon effect disappears or even reverses (e.g., Proctor and Lu, 1999; Tagliabue et al., 2000; Rubichi et al., 2005; Iani et al., 2009; Lugli et al., 2013). This is thought to occur because the short-term associations between a stimulus location and the incompatible response that were created in order to perform the spatial compatibility task remain active and influence performance in the subsequent Simon task, hence contrasting the overlearned long-term associations (see Pellicano et al., 2010 for the effects of overlearned long-term associations). Interestingly, this "transfer of learning" effect occurs even when the practice task is observed and not performed (Iani et al., 2013). In contrast, practicing with a spatially compatible mapping does not affect the Simon effect hence suggesting that long-term links cannot be further improved by training.

By using a similar paradigm, Bae et al. (2009, Experiment 1) showed that prior practice with an orthogonal spatial compatibility task influences the orthogonal Simon effect with the two mappings exerting equal influences: a positive orthogonal Simon effect (that is, an advantage for the up-right/down-left relation) was found when participants practiced with the up-right/down-left mapping, while a reversed effect (that is, an advantage for the up-left/down-right relation) was found when participants practiced with the up-left/down-right mapping. The authors interpreted this result as an indication that the long-term links between codes of corresponding polarity are weaker than the long-term links between corresponding S-R locations influencing performance in the parallel Simon task.

A way to investigate the strength of these links is to assess whether they vary as a function of steady human features such as handedness. Manual laterality is considered as a defining characteristic of our species. It is indeed estimated that about 90% of the population prefers the right arm to the left when reaching for a target or manipulating objects (e.g., Peters, 1998; see Goble and Brown, 2008 for a review). Since manual laterality affects the way we interact with the world, it has been proposed that it also affects the way we represent information (e.g., Casasanto, 2009, 2011). Specifically, it has been shown that handedness influences external space representation (e.g., Sampaio and Chokron, 1992). Furthermore, it has been shown that individuals implicitly associate concepts with positive emotional valence with the side of body they could use more fluently (Casasanto, 2009). As regards, spatial compatibility effects, there is experimental evidence that the parallel Simon effect is influenced by handedness, with an advantage of the dominant hand when it executes a response in the corresponding space (e.g., Rubichi and Nicoletti, 2006; see also Rabbit, 1978; Peters, 1981). Ladavas (1987) demonstrated that also the orthogonal spatial S-R compatibility effect is affected by participants' handedness. In her study, right-handed and left-handed participants performed an orthogonal spatial compatibility task in which upper and lower stimuli were mapped with left and right responses (the right hand pressed a right button and the left hand pressed a left button). Results showed better performance when both right-handers and left-handers participants responded to upper stimuli with the dominant hand and to lower stimuli with the non-dominant hand. That is, right-handed participants showed an advantage for the up-right/down-left mapping, whereas left-handers participants showed an advantage for the up-left/down-right mapping. The author explained these findings by postulating the existence of an asymmetry in the coding of the dominant and non-dominant hands along the vertical dimension with the dominant hand being represented as "up" and the non-dominant hand as "down", irrespective of their actual position.

Based on the evidence described above, the present study was aimed at assessing whether handedness affects the orthogonal Simon effect and whether in left-handers the orthogonal Simon effect can be modulated by the type of mapping experienced in a prior orthogonal spatial compatibility task in which stimulus position was relevant. To this end, in Experiment 1, we assessed the orthogonal Simon effect in a group of right-handed participants and in a group of left-handed participants. In Experiment 2, we assessed whether the orthogonal Simon effect is influenced by the S-R mapping used for an orthogonal spatial S-R compatibility task performed 5 min before, irrespective of handedness.

EXPERIMENT 1

As stated in the Introduction, the results by Ladavas (1987) indicate that, when stimulus position is task relevant, left-handers show a preferential association of the dominant hand with upper visual stimuli and of the non-dominant hand to lower visual stimuli. The aim of Experiment 1 was to assess whether, similarly to right-handers, left-handers show a preferential association of the dominant hand with upper visual stimuli and of the non-dominant hand to lower visual stimuli even when the stimulus position is task irrelevant.

Based on the results by Ladavas (1987) and according to the asymmetric coding account, we expected left-handers to show better performance when upper stimuli demand a left response and lower stimuli demand a right response. The finding of a reversed orthogonal Simon effect for left-handers would support the idea that the associations of stimulus and response codes of corresponding polarity are "hard wired".

METHOD

Participants

Forty undergraduate students of the University of Modena and Reggio Emilia took part in the experiment for either payment (7€) or course credit. Hand preference was assessed according to the Edinburgh Handedness Inventory (Oldfield, 1971) that produces scores ranging from +100 and –100. Twenty students were classified as right-handed (mean manual preference: 77.6, SD = 20.53; age range:19–30 years; 12 female) and twenty as left-handed (mean manual preference: –56.3, SD = 36.33; age range: 21–40 years; 12 female). Participants were naïve about the purpose of the study and reported having normal or corrected-to-normal visual acuity. The experiment was conducted in accordance with the guidelines laid down in the Declaration of Helsinki.

Apparatus and stimuli

Participants sat in front of a color monitor controlled by an IBM computer, in a dimly illuminated room, at a viewing distance of approximately 57 cm. The eyes were aligned to the center of the screen.

Stimulus presentation and response collection were controlled by E-prime software (Schneider et al., 2002). Stimuli were red or green squares (1.3° × 1.3°), which were randomly, presented 4° above or below a central white fixation cross (0.5° × 0.5°) on a dark background. Responses were executed by pressing the "D" and "L" keys on a standard keyboard with the left and right index fingers.

Procedure

Trials began with presentation of the fixation cross, accompanied by a 800 Hz warning tone. After 1 s, the imperative stimulus appeared above or below the fixation cross and remained visible-for 1500 ms. The response terminated the trial. A 400-Hz tone was given for 500 ms following either an incorrect response or a late response (longer than 1500 ms). The next trial began 500 ms after the response or the feedback.

Participants were required to respond as quickly and accurately as possible to the color of the stimulus. Half of the right-handed and half of the left-handed participants responded to the red square with the right key and to the green square with the left key, the remaining participants experienced the opposite S-R mapping.

The task consisted of 360 trials divided in three blocks of 120 trials each, preceded by 24 practice trials.

RESULTS

Responses that were 2 standard deviations above or below the participant's mean were excluded from the analyses (3.5% of total trials).

Mean correct RTs and percentage of error (PE) were calculated for each participant as a function of correspondence (up-right and down-left mappings as corresponding; up-left and down-right mappings as non-corresponding) and submitted to two separate repeated-measures analyses of variance (ANOVA) with correspondence as within-subject factor and handedness (right-handers vs. left-handers) as between-subjects factor. Paired sample *t*-tests were employed as *post hoc* tests and the Bonferroni correction was applied so that the *p*-level was decreased to 0.025 for the first order interactions. The respective data are shown in **Table 1**.

Table 1 | Experiment 1.

	Up-right/ down-left mapping	Up-left/ down-right mapping	Orthogonal Simon effect
Right-handers	405 (94.9)	407 (95.7)	2
Left-handers	390 (83.9)	383 (81.5)	−7

Mean reaction time (and standard deviation) in ms for the orthogonal Simon task as a function of handedness (right-handers and left-handers), and mapping (up-right/down-left and up-left/down-right). The orthogonal Simon effect is computed as the difference between RTs in the up-left/down-right mapping and RTs in the up-right/down-left mapping.

As regards RTs, the main effects of handedness, $F(1,38) = 1.81$, $p = 0.19$, and correspondence, $F(1,38) = 1.33$, $p = 0.25$, did not reach statistical significance. The interaction between correspondence and handedness reached significance, $F(1,38) = 4.55$, $p < 0.05$. *Post hoc* comparisons showed that for left-handers non-corresponding responses (383 ms) were significantly faster than corresponding responses (390 ms; $p < 0.025$). The difference between corresponding (405 ms) and non-corresponding (407 ms) responses did not reach significance for right-handers.

Overall PE was 4.7%. No significant main effect or interaction reached significance.

Our results showed that the orthogonal Simon effect significantly differed in the two groups, with left-handers showing a 7-ms advantage for the up-left/down-right mapping compared to the up-right/down-left mapping (that is, a reversed orthogonal Simon effect). These data suggest that a steady human feature such as handedness influences the polarity attributed to stimulus and response codes.

The finding of a non-significant effect for right-handers is not surprising. Indeed, previous studies assessing the orthogonal Simon effect in right-handers found an effect ranging from 3 to 12 ms (e.g., Nishimura and Yokosawa, 2006; Cho et al., 2008), thus suggesting that the long-term associations at the basis of this effect are not as strong as those responsible for the parallel Simon effect.

EXPERIMENT 2

The main aim of the present experiment was to assess whether in left-handers the orthogonal Simon effect can be modulated by the type of mapping experienced in a prior orthogonal spatial compatibility task in which stimulus position was relevant. To this aim, right- and left-handers practiced an orthogonal spatial compatibility task with either an up-right/down-left or an up-left/down-right mapping. After a 5 min interval, they performed an orthogonal Simon task, in which stimulus color was relevant while stimulus position was irrelevant.

METHOD

Participants

The same participants of Experiment 1 took part to Experiment 2. The time interval between the two experiments was 2 weeks.

Participants for each handedness group were randomly assigned to the two different practice-mapping conditions: up-right/down-left mapping and up-left/down-right mapping. The experiment was conducted in accordance with the guidelines laid down in the Declaration of Helsinki.

Apparatus, stimuli and procedure

The apparatus was the same as in Experiment 1. Stimuli for the orthogonal spatial compatibility task were white squares (1.3° × 1.3°), randomly presented 4° above or below a central white fixation cross (0.5° × 0.5°) on a dark background. Responses were executed by pressing the "D" and "L" keys on a standard keyboard with the left and right index fingers. Stimuli and response keys for the orthogonal Simon task were the same used in Experiment 1.

Participants performed the orthogonal spatial compatibility task (from now on, practice session) followed, after a 5-min interval, by the same orthogonal Simon task (from now on, transfer session) performed in Experiment 1.

In the practice session, each trial began with the presentation of the fixation cross accompanied by a sound, followed after 500 ms by the imperative stimulus which was randomly shown above or below the fixation until a response was given, but anyway no longer than 1 s. A 400-Hz tone was given for 500 ms as feedback in case of errors: responses performed with the wrong key or slower than 1000 ms. The inter-trial interval was of 500 ms. Participants were required to respond as quickly and accurately as possible to stimulus position. 20 participants (10 right-handers and 10 left-handers) practiced with the up-right/down-left mapping; while the remaining 20 participants practiced with the up-left/down-right mapping. In the transfer session, participants performed the same orthogonal Simon task performed in Experiment 1, with the same mapping rule used in the first session.

The practice task consisted of 300 trials divided into three blocks of 100 trials each, preceded by 10 practice trials, while the transfer task consisted of 360 trials divided in three blocks of 120 trials each, preceded by 24 practice trials.

RESULTS

Only the data for the Simon task were analyzed. For each participant, RTs shorter and longer than 2 standard deviations from the mean were excluded from the analyses (3.8% of the total trials).

Correct RTs and PE were submitted to two separate repeated-measures ANOVA with correspondence (up-right and down-left mappings as corresponding; up-left and down-right mappings as non-corresponding) as a within-subject factor, and practice mapping (up–right/down–left; up–left/down–right) and handedness as between-subjects factors. Paired sample *t*-tests were employed as *post hoc* tests and the Bonferroni correction was applied so that the *p*-level was decreased to 0.025 for the first order interactions. The respective data are displayed in **Table 2**.

Overall, left-handers were 20-ms faster than right-handers, as indicated by the main effect of handedness, $F(1,36) = 9.17$, $p < 0.01$. The main effects of correspondence, $F < 1$, and practice mapping, $F < 1$, did not reach statistical significance, however, they significantly interacted, $F(1,36) = 54.56$, $p < 0.01$. *Post hoc* tests showed that for the participants who practiced the up-right/down-left mapping, corresponding responses (389 ms) were significantly faster than non-corresponding responses (404 ms), this resulting in a 15-ms orthogonal Simon effect ($p < 0.001$). For the participants who practiced the up-left/down-right mapping, corresponding responses (403 ms) were significantly slower than non-corresponding responses (386 ms), this resulting in a 17-ms reversed orthogonal Simon effect ($p < 0.001$). Interestingly, this pattern of results was evident irrespective of handedness, as indicated by the lack of a significant correspondence × practice mapping × handedness interaction, $F < 1$.

Overall PE was 4.3%. The analysis revealed only a significant correspondence × practice mapping interaction, $F(1,36) = 21.20$, $p < 0.001$. For the participants who practiced with the up-right/down-left mapping, responses were more accurate on up-right/down-left trials than on up-left/down-right trials (2.7% and 5.7% of errors, respectively, $p < 0.01$). For participants who practiced the up-left/down-right mapping, responses were more accurate on up-left/down-right trials than on up-right/down – left trials (2.5% and 6.2% of errors, respectively, $p < 0.01$). This two-way interaction was not modulated by handedness, $F < 1$.

Our results are consistent with the findings of Bae et al. (2009) in showing that the orthogonal Simon effect is influenced by the S-R associations between vertical stimulus positions and horizontal response locations established during practice on an orthogonal spatial compatibility task. Specifically, the orthogonal Simon effect was of 15 ms after practice with the up-right/down-left mapping and reversed to –17 ms after practice with the up-left/down-right mapping. Interestingly, practice with the up-right/down-left mapping increased the size of the orthogonal Simon effect in both right- and left-handers. Similarly, the up-left/down-right mapping reversed the effect in both right- and left-handers. Hence, it seems that the short-term S-R associations established during practice are strong enough to override the long-term associations responsible for the effect evident before performing the practice and that these long-terms associations are not unchangeable as those responsible for the parallel Simon effect.

Table 2 | Experiment 2.

Practice mapping	Up-right/ down-left	Up-left/ down-right	Orthogonal Simon effect
Right-handers			
Up-right/down-left	406 (98.0)	424 (93.9)	18
Up-left/down-right	422 (99.9)	404 (93.2)	−18
Left-handers			
Up-right/down-left	372 (80.5)	383 (88.8)	11
Up-left/down-right	384 (79.8)	367 (71.7)	−17

Mean reaction time (and standard deviation) in ms for the orthogonal Simon task as a function of practice mapping (up-right/down-left and up-left/down-right) and Simon mapping (up-right/down-left and up-left/down-right) for right- (top panel) and left-handers (bottom panel).The orthogonal Simon effect is computed as the difference between RTs in the up-left/down-right mapping and RTs in the up-right/down-left mapping.

COMPARISON BETWEEN EXPERIMENTS

To further investigate the effect of the practice mapping, we submitted correct RTs of the two experiments to a repeated-measures ANOVA with practice mapping (up-right/down-left; up-left/down-right) and handedness as between-subject factors and correspondence (up-right and down-left mappings as corresponding; up-left and down-right mappings as non-corresponding) and session (Experiment 1 as session 1 and Experiment 2 as session 2) as within-subject factors. Paired sample *t*-tests were employed as *post hoc* tests and the Bonferroni correction was applied so that the *p*-level was decreased to 0.025 for the first order interactions.

This analysis revealed a significant main effect of handedness, $F(1,36) = 5.09$, $p < 0.05$, with faster RTs for left-handers (382 ms) than for right-handers (410 ms), and significant interactions between practice mapping and correspondence, $F(1,36) = 26.62$, $p < 0.001$, and between session, practice mapping, and correspondence, $F(1,36) = 36.92$, $p < 0.001$. Handedness did not interact with any factor. No other main effect or interaction reached statistical significance.

To further assess the three-way interaction, we performed separate analyses by practice mapping. These analyses showed that for the up-right/down-left practice mapping, the main effect of correspondence, $F(1,18) = 13.38$, $p < 0.01$, and the interaction between session and correspondence, $F(1,18) = 21.97$, $p < 0.001$, were significant. *Post hoc* comparisons indicated that the difference between corresponding and non-corresponding trials was significant only in Session 2, with corresponding trials (389 ms) being faster than non-corresponding trials (403 ms; $p < 0.001$). The main effect of correspondence, $F(1,18) = 14.05$, $p < 0.01$, and the interaction between session and correspondence, $F(1,18) = 17.73$, $p < 0.01$, were significant also for the up-left/down-right mapping. *Post hoc* comparisons indicated that the difference between corresponding and non-corresponding trials was significant only in Session 2, with non-corresponding trials (386 ms) being faster than corresponding trials (403 ms) ($p < 0.001$).

These results confirmed that practice with the up-right/down-left mapping increased the size of the orthogonal Simon effect in both right- and left-handers. Similarly, the up-left/down-right mapping reversed the effect in both right- and left-handers.

GENERAL DISCUSSION

The aim of the present study was to assess whether the orthogonal Simon effect evident in right- and left-handers is affected in a similar way by the S-R mapping used in a prior orthogonal spatial compatibility task. Experiment 1 was designed to assess the orthogonal Simon effect in right-handed and left-handed participants, while Experiment 2 was aimed at assessing whether, for both sub-groups, the effect is influenced by the S-R mapping used for an orthogonal spatial S-R compatibility task performed 5 min before.

Our results showed that the orthogonal Simon effect significantly differed in left-handed compared to right-handed participants. While right-handers showed no reliable effect, left-handers showed an advantage for the up-left/down-right mapping (Experiment 1). This result supports the existence of asymmetries in spatial coding in both the vertical and horizontal dimension, which can be represented as polarity differences. As stated in the Introduction, stimulus and response alternatives with binary values are coded as having a positive or a negative polarity (e.g., Proctor and Cho, 2006). As regards the vertical dimension, there is indication that above tends to be coded as positive, and below as negative in vertical spatial representation, as also demonstrated by the finding that above positions are processed faster than below positions (e.g., Chase and Clark, 1971). As regards the horizontal dimension, right-handers code right as positive and left as negative, as suggested by faster processing of right positions as compared to left positions (e.g., Olson and Laxar, 1973, 1974). The findings of the present study, along with those of Nishimura and Yokosawa (2006) are consistent with the idea that handedness influences how we interact with the world and, as a consequence, the way we code and represent information (Casasanto, 2009) since they showed that the horizontal spatial representation is strongly affected by handedness. More precisely, the observation that, in the absence of prior practice, an advantage of the up-left/down-right mapping emerges for left-handers suggests that, differently from right-handers, they code left as positive and right as negative. While in right-handers the stimulus code of the above position automatically activates the right-response code that is the response code with the same polarity, in left-handers it automatically activates the left response code. Similarly, the stimulus code of the below position automatically activates the left response code in right-handers and the right response code in left-handers.

Interestingly, we showed that this tendency might be affected by prior practice. Indeed, the orthogonal Simon effect was strongly influenced by prior practice regardless of the participants' handedness (Experiment 2). These results suggest that the long-term associations between stimulus and response codes of the same polarity established on the basis of handedness are weaker than the long-term spatially corresponding associations between stimulus and responses, which are thought to be overlearned or even genetically determined (e.g., Pellicano et al., 2010). Indeed, differently from the latter, that are unaffected by practice, long-term polarity associations can be easily overridden by the short-term S-R associations acquired during practice. To note, a recent study by Stock et al. (2013) showed that spatial aspects of a task can change patterns of information processing with spatial information being flexibly allocated to the two hemispheres of the brain. The results of the present study further extend this finding by showing that the flexible spatial representations formed during the practice session may affect how a subsequent (transfer) task is performed.

The finding that after practice left-handers displayed the same behavior as right-handers may be explained by invoking the asymmetries in lateralization observed between right- and left-handers. The results of several studies indicate that in hand motor skills right-handers show a stronger lateralization than left-handers, with right-handers relying more on their dominant hand as compared to left-handers who seem to equally rely on both hands (e.g., Kilshaw and Annett, 1983; Geschwind and Galaburda, 1987; Gonzalez et al., 2007; Linkenauger et al., 2009). In line with these findings, it has been shown that in right-handers the cortical representations of the right arm and hand are larger in the left-hemisphere than in the right hemisphere, while in left-handers there is a symmetrical representation

across hemispheres (e.g., Linkenauger et al., 2009). Furthermore, there is recent evidence that cerebral laterality for spatial cognition differs between these two subgroups (Shimoda et al., 2008). Taken together, these differences in lateralization may explain why prior practice with a spatial compatibility task neutralized the differences in performance between right- and left-handers.

To conclude, the present data indicate that handedness might affect the way we code spatial information favoring specific associations between stimuli and responses that affect automatic response activation. However, short-term S-R associations acquired during a prior practice can easily override these associations established on the basis of a steady human feature such as handedness.

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"Right on all occasions?" – On the feasibility of laterality research using a smartphone dichotic listening application

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Most psychological experimentation takes place in laboratories aiming to maximize experimental control; however, this creates artificial environments that are not representative of real-life situations. Since cognitive processes usually take place in noisy environments, they should also be tested in these contexts. The recent advent of smartphone technology provides an ideal medium for such testing. In order to examine the feasibility of mobile devices (MD) in psychological research in general, and laterality research in particular, we developed a MD version of the widely used speech laterality test, the consonant-vowel dichotic listening (DL) paradigm, for use with iPhones/iPods. First, we evaluated the retest reliability and concurrent validity of the DL paradigm in its MD version in two samples tested in controlled, laboratory settings (Experiment 1). Second, we explored its ecological validity by collecting data from the general population by means of a free release of the MD version (*iDichotic*) to the iTunes App Store (Experiment 2). The results of Experiment 1 indicated high reliability ($r_{ICC} = 0.78$) and validity ($r_{ICC} = 0.76$–0.82) of the MD version, which consistently showed the expected right ear advantage (REA). When tested in real-life settings (Experiment 2), participants ($N = 167$) also showed a significant REA. Importantly, the size of the REA was not dependent on whether the participants chose to listen to the syllables in their native language or not. Together, these results establish the current MD version as a valid and reliable method for administering the DL paradigm both in experimentally controlled as well as uncontrolled settings. Furthermore, the present findings support the feasibility of using smartphones in conducting large-scale field experiments.

Keywords: laterality, dichotic listening, language lateralization, smartphone, mobile device, software application

INTRODUCTION

Traditionally, the laboratory functions as center stage for psychological experiments in general, and laterality research in particular. Although this has obvious advantages, it is often too resource demanding to reach a larger audience and obtain a broad sample. In experimental psychological research the control of confounding variables is weighed against the degree of ecological validity; usually aiming to maximize control at the expense of ecological validity (Brunswik, 1947). However, the advent of handheld mobile devices (MDs; e.g., smartphones) with processing power comparable to stationary systems has opened the door to transferring experiments from the laboratory to real-life settings while maintaining control over stimulus presentation. In real-life, cognitive processes are executed in noisy environments. Thus, the natural environment is the authentic arena where psychological theories can be proven to transcend laboratory walls and stand the test of real-life situations. This approach is not entirely new; however, until recently, it has been promoted mainly within a clinical context where it is referred to as ambulatory assessment involving the acquisition of psychophysiological data and self-reports in natural settings (e.g., Fahrenberg, 1996). While the popularity of internet-based psychological testing has grown rapidly over the last decade (see, Barak and Buchanan, 2004), the use of MDs for data collection is still in its infancy. One clear advantage of using MDs over internet-based testing that relies mostly on stationary computers is the possibility to access participants over the whole day, anywhere that they happen to be at that particular time, allowing for unique opportunities for experimental intervention. Some recent studies have harnessed this advantage by acquiring participants' self-reports on their current mood (Courvoisier et al., 2010) as well as their cognitive performance at controlled time points during the day (Tiplady et al., 2009; Kennedy et al., 2011). While these studies include a fixed sample with a mainly clinical focus, there are also those that use open "recruitment" of participants through a software application that can be downloaded and consequently reach a larger audience (crowd sourcing) than what is normally achieved with common sampling methods (e.g., Killingsworth and Gilbert, 2010; Dufau et al., 2011). A review of various types of behavioral data collection using smartphone technology and their limitations is presented by Miller (2012).

The objective of the present experiments was to examine the feasibility of paradigms implemented via MDs for the purposes of

laterality research. For this purpose, we chose a classical speech laterality test, namely, dichotic listening (DL; Bryden, 1988; Hugdahl, 2003, 2011); a test which has been used in laboratories around the world for decades (see, Hugdahl, 2011). The history of the DL paradigm in laterality research goes back half a century to research conducted by Kimura (1961, 2011), who found that when simultaneously presented with two verbal stimuli, one to the left ear (LE) and the other to the right ear (RE), participants exhibit the tendency to report the RE stimulus more often than the LE stimulus (the so-called RE advantage, REA). This finding is commonly interpreted as an indicator of left hemisphere processing of language (e.g., Kimura, 1967; Pollmann, 2010). Support for this interpretation of the REA comes from studies using functional magnetic resonance imaging (e.g., Jäncke et al., 2002; van den Noort et al., 2008), positron emission tomography (e.g., O'Leary et al., 1996; Hugdahl et al., 1999), electroencephalography (e.g., Brancucci et al., 2004), magnetoencephalography (e.g., Alho et al., 2012), Wada-test (e.g., Hugdahl et al., 1997), as well as from studies on split brain patients and patients with callosal lesion (e.g., Milner et al., 1968; Springer and Gazzaniga, 1975; for a review see Westerhausen and Hugdahl, 2008). There are a number of variants of the DL test mainly differing in the stimulus material used. In the present study, we used the consonant-vowel (CV) paradigm (Shankweiler and Studdert-Kennedy, 1967; Hugdahl and Andersson, 1986), which according to a meta-analysis by Voyer (1998) produces the most reliable laterality effects, with reliability ranging from 0.61 (Bryden, 1975; split-half reliability, Spearman r) to 0.91 (Wexler et al., 1981; test-retest, Pearson r).

For the present project, we developed a MD version of the DL test (*iDichotic*) for the iPhone/iPod touch and tested it in two steps. First, we used it in a controlled laboratory setting where we evaluated the validity and reliability of the DL paradigm in its MD version (Experiment 1). Second, we investigated whether the MD version produces robust results when applied to the general population as part of a "crowd sourcing" field experiment (Experiment 2), by making the paradigm publicly available on Apple's digital application distribution platform (App Store).

EXPERIMENT 1

In the first experiment, reliability of the MD version of the DL paradigm was assessed in a Norwegian sample as well as an Australian sample, to test the intercultural transfer of results. For this purpose, we adopted a test-retest design according to Cohen et al. (1996), in which participants were tested twice with the same version of the paradigm and performing the same task, and then calculated the correlation of laterality indices from each time point. In addition, concurrent validity of the MD version was tested by using the results of the standard personal computer (PC) version as "criterion." The results of the PC version were used as criterion since it represents the current standard procedure for measuring speech laterality as conducted in our laboratories and most others (Hugdahl, 2003).

MATERIALS AND METHODS

Participants

The Norwegian sample included 33 healthy, subjects with a mean age of 31.7 years (SD = 9.8) including 22 female and 11 male participants. The Australian sample included 43 healthy, female subjects with a mean age of 21.6 years (SD = 2.7). The exclusion criteria were as follows: left-handedness (self-report), more than three homonym errors (see below), less than six overall correct reports, and more than 20% hearing asymmetry at either time point (inferred from hearing test results administered as part of the application). Participants gave written informed consent.

Material and procedure

The stimulus material was based on the standard Bergen DL paradigm (Hugdahl, 2003), using the six CV syllables/ba/, /da/, /ga/, /ta/, /ka/, and /pa/ as stimulus material. The stimuli were pairwise, dichotically presented CV syllables via headphones/earphones, and in all possible pairwise combinations yielding a total of 36 pairs, also including six homonym pairs with the same syllable presented to the LE and RE. The syllables used for the Norwegian sample were spoken by a native, male Norwegian speaker with constant intonation and intensity, and had a mean duration between 400–500 ms. Likewise, the Australian sample was correspondingly tested with syllables spoken by a native, male English speaker, and had a mean duration between 480–550 ms. The syllables in each pair were temporally aligned to each other for simultaneous onset of their initial stop-consonants. The MD version included a hearing test to control for hearing asymmetries, which can bias the results toward the right or LE. In this test the loudness of a 1000 Hz tone had to be regulated using a horizontal volume scroll bar to indicate when tone is just inaudible (separate for LE and RE).

In the Norwegian sample each participant completed the test four times, twice as the standard PC version, and twice using the MD version (see below). The order of the four test runs was inter-individually balanced using an ABBA design. Participants in the Australian sample undertook two consecutively presented test runs only using the MD version of the paradigm.

For both samples, a test run consisted of the presentation of a full set of 36 stimulus pairs, which were pseudo-randomly presented with a 4000 ms inter-stimulus interval. Within the interval between stimulus presentations participants were asked to respond manually, either by key press for the PC implementation or by using the touch screen of the MD. There were six labeled buttons on the keyboard and six buttons on the touch screen, respectively, one for each syllable used in the test. Regardless of mode of implementation only one answer was possible per trial. The instructions followed free-report instruction (non-forced condition, cf. Hugdahl, 2003); that is, participants were instructed to listen to the syllables and report after each trial which syllable they heard best. An answer was considered to be "correct" when the response matched either right or the LE stimulus in that particular trial; it was counted as "error" when the chosen syllable had not been presented or when no response was given. The subjects did not get feedback about their performance until the end of the experiment.

Stimulus administration was delivered via Sennheiser headphones for the PC version and via the standard Apple earphones for the MD version. In view of the potential for differences in the quality of the output, especially with regard to the possibility of asymmetric presentation of the stimuli, we recorded a white noise spectrogram from the two types of headphones. The right-left

mean differences within the frequencies relevant for speech (250 Hz–2 kHz) were −0.12 dB for the Sennheiser headphones and 0.32 dB for the Apple earphones. In light of previous research, showing that only inter-aural differences above 6 dB affect the magnitude of the ear advantage (Hugdahl et al., 2008), we considered the present differences of well below 1 dB to be negligible.

For each test run, the number of correct responses of LE and RE stimuli was recorded and used to determine a laterality index (LI) calculated according to the following formula: $LI = [(RE - LE)/(RE + LE)] \times 100$. Thus, the LI expresses the percentage difference between the correct LE and RE reports with positive values indicating a right, and negative values a LE advantage.

Instruments

The PC version of the CV-DL paradigm was programmed and run in E-prime (Version 2; Psychology Software Tools, http://www.pstnet.com/). The MD version was developed in Xcode 3.2.5 using the iOS software development kit (Apple Inc., Cupertino, CA) and administered on iPhone or iPod touch units running as a prototype version of the final *iDichotic* application (see Experiment 2).

Statistical analysis

Intraclass correlation analyses [ICC(3,1), see Shrout and Fleiss, 1979] were conducted to determine reliability and validity of the MD version. For data from both samples, reliability was determined as retest reliability and obtained by correlating the LI of the two test runs using the MD version. Additionally, for the Norwegian sample, reliability was calculated for the results of the PC version. Validity of the MD version was assessed within the Norwegian sample data by calculating the intraclass correlation between the results of the two test runs with the MD version and the results of the standard PC version. Here, the mean LI of the two test runs via the PC version was used as criterion.

Additional analyses were conducted in order to test for mean differences between the two DL versions and the effect of test repetition on the LI (dependent variable). In the Norwegian sample, a 3-way analysis of variance (ANOVA) with within-subject factors *Version* and *Timepoint,* as well as between-subject factor *Sex*. Comparably, for the Australian sample, a *t*-test was calculated to compare the mean LI across the two test runs. The above analyses were supplemented with one-sample *t*-tests against zero to test for significant LI, i.e., REA, and an independent-samples *t*-test comparing the total mean LI of the Norwegian sample with the total mean LI of the Australian sample. In order to further investigate the differences between the samples, we conducted two *post hoc* analyses. First, to examine possible sex effects, only the females of both groups were compared. Second, to address possible effects of the presentation device, only the results collected with the MD version were compared.

For all analyses, level of significance was set to $\alpha = 0.05$ and effect sizes were provided as measures of explained variance (η^2), or as standardized mean difference (Cohen's *d*). Statistical analyses were performed in PASW 18.0 (IBM SPSS, New York, USA).

RESULTS

The retest reliability was identical in both the Norwegian and the Australian sample (both $r_{ICC} = 0.78$) and slightly higher than the reliability of the PC version ($r_{ICC} = 0.70$; Norwegian sample only; see also **Figures 1** and **2**). Validity, tested in the Norwegian sample by correlating the results of MD and PC version (see **Figure 3**) was slightly higher for test run 2 ($r_{ICC} = 0.82$) than for test run 1 ($r_{ICC} = 0.76$).

The ANOVA conducted for the Norwegian sample revealed main effects of *Version* [$F(1,31) = 8.64$, $p = 0.01$, $\eta^2 = 0.023$, MD > PC] and *Timepoint* [$F(1,31) = 4.40$, $p = 0.04$, $\eta^2 = 0.014$, test run 2 > test run 1]. Neither the interaction of the within-subjects factors [$F(1,31) = 0.004$, $p = 0.81$, $\eta^2 < 0.001$], nor the main effect of the between-subject factor of Sex [$F(1,31) = 0.001$, $p = 0.98$, $\eta^2 < 0.001$] were significant. In the Australian sample there was no significant difference between the two test runs [$t(42) = -1.10$, $p = 0.28$, $d = -0.11$].

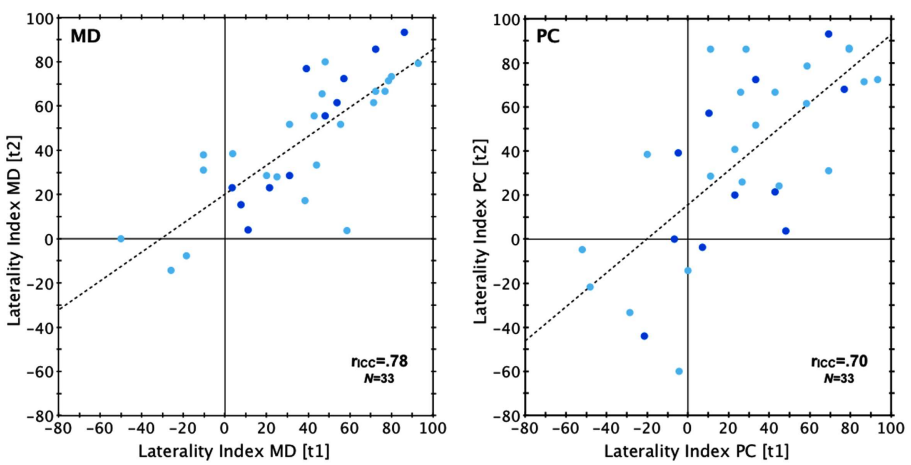


FIGURE 1 | Reliability (Norwegian sample). Scatterplot depicting intraclass correlations between results at test run 1 (t1) and test run 2 (t2; left: MD version; right: PC version). Laterality index, percentage difference between correct LE and RE reports. r_{ICC}, intraclass correlation coefficient. Dot color indicates sex: light blue, females; dark blue, males.

A REA was found for both versions of the DL paradigm and in both samples. In the Norwegian sample, the MD version produced a LI of 36.5% ± 35.3 (test run 1) and 44.2% ± 29.3 (test run 2), while the PC version produced a LI of 27.2% ± 38.5 (test run 1) and 36.3% ± 41.9 (test run 2). Each of these LIs was significantly larger than zero [all $t(32) > 4.06$, all $p < 0.001$, $d = 0.71$–1.51]. As for the Australian sample, the LI was 9.2% ± 27.2 (test run 1) and 12.3% ± 29.4 (test run 2), both significantly larger than zero [test 1: $t(42) = 2.21$, $p = 0.03$, $d = -0.34$; test 2: $t(42) = 2.75$, $p = 0.01$, $d = 0.42$]. For an overview of the correct ear scores and laterality indices for both samples see **Table A1** in Appendix. A comparison of the mean LI across all test runs and versions of the Norwegian sample (LI = 36.0% ± 32.5) against the mean LI across both test runs of the Australian sample (LI = 10.8 ± 26.8) revealed that the Norwegian sample had a significantly stronger REA [$t(74) = 3.7$, $p < 0.01$, $d = 0.85$]. Comparing only the females of both samples still showed a significantly larger LI in the Norwegian sample [Norwegian sample: 36.1% ± 34.5; Australian sample: 10.8 ± 26.8; $t(63) = 3.3$, $p < 0.01$, $d = 0.82$]. Also when only MD results were compared, the Norwegian sample had a significantly larger LI [Norwegian sample: 40.3% ± 30.6; Australian sample: 10.8 ± 26.8; $t(74) = 4.5$, $p < 0.001$, $d = 1.03$].

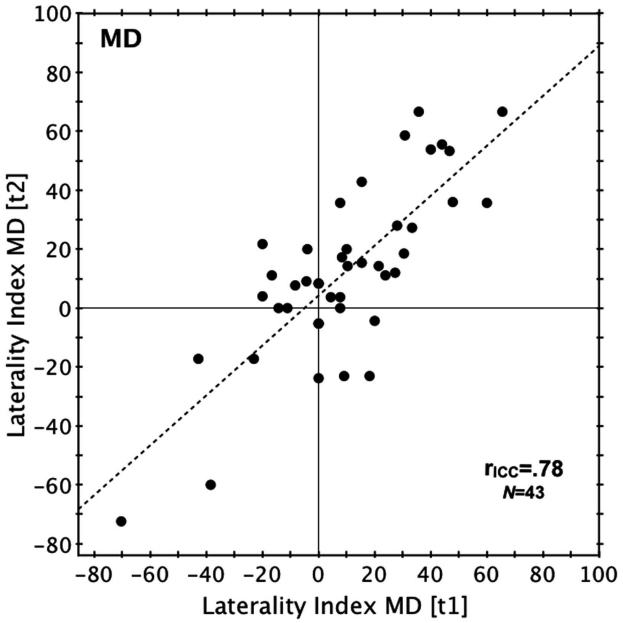


FIGURE 2 | Reliability (Australian sample). Scatterplot relating the LI of the first and second test run in the Australian sample. Laterality index, percentage difference between correct LE and RE reports. r_{ICC}, intraclass correlation coefficient.

DISCUSSION

The results from the Norwegian and Australian samples indicate that the MD version of the DL paradigm produces highly reliable results, with intraclass correlation coefficients slightly higher than that obtained via the PC version in the Norwegian sample. With an intraclass correlation of 0.78 the reliability of the MD version is well within the range usually found in studies using CV DL paradigms (i.e., between 0.61 and 0.91, cf. Voyer, 1998). Hugdahl and Hammar (1997), using the same DL paradigm on a Walkman, showed a medium-strong correlation coefficient of 0.61. The authors used a test-retest interval of 2 weeks compared to the present consecutive administration, which may explain the higher correlation in the present study. We also assessed criterion validity in the Norwegian sample and it appears to be high, as indicated by strong correlations between the results of both MD-based test runs along with the results obtained with the standard PC version.

Beyond demonstrating high reliability and validity, the findings revealed some results that deserve further discussion. First, as indicated by a significant main effect in the Norwegian sample, the second test run produced a stronger REA than the first, irrespective of whether MD or PC version was applied. This effect might be due to practice, habituation effects, or a general familiarization with stimulus material and testing procedure. For example, practice effects have been shown to increase performance and reverse laterality in a mental rotation task (Voyer et al., 1995). Nevertheless, the *Timepoint* effect was small (2.3% explained variance) and was not replicated in the larger Australian sample.

A second interesting observation in the Norwegian sample was that the MD produced a stronger REA than the PC version. However, this effect was also small, accounting for only 2% of the variance in the dependent variable. Assuming that the MD and PC version did not produce a systematic effect on laterality in terms of output level (see spectrogram test in Materials and Methods section), one possible reason for the version effect might be found by considering the responses that were required. While the MD version required participants to hold the device in the right hand and respond with the right thumb, the PC version used response keys distributed on a keyboard to be used with fingers of the right hand. This might result in differential demands for the visual-motor coordination, differentially favoring left or right hemispheric processing, and thus indirectly affecting the laterality as measured with the DL paradigm. However, without further evidence any such interpretation remains speculative, and as pointed out above, the effect was rather small, hence not substantially affecting the reliability measures which, calculated as ICC(3,1), also incorporate mean differences in the reliability calculations (cf. Shrout and Fleiss, 1979).

Finally, the MD version in the female-only, Australian sample produced a smaller REA than both versions in the Norwegian sample, suggesting that factors such as native language background and sex of the subjects may contribute to the magnitude of the REA. Indeed, a comparison of the mean LI obtained with similar DL studies conducted in several countries with different languages, indicates that the REA might be smaller in English speakers [LI of about 14% in Hirnstein (2011)] than in Norwegian (about 26%, Rimol et al., 2006) or German speakers (about 30%; Westerhausen et al., 2006). With regard to sex, the REA is frequently found to be more pronounced in male as compared to female subjects (e.g., Lake and Bryden, 1976; Zatorre, 1979; Cowell and Hugdahl, 2000; for a review see Voyer, 2011). Thus, in view of differences in both the sex distribution and language background across the two samples, a stronger LI in the Norwegian sample

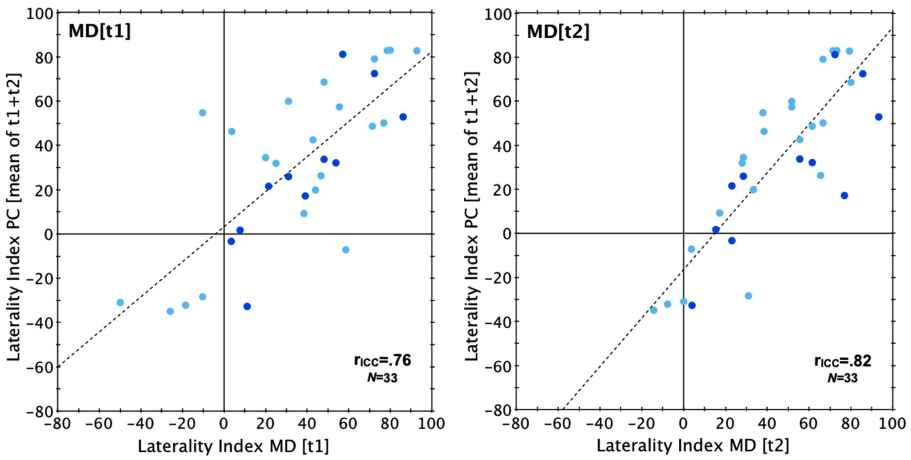


FIGURE 3 | Validity. Scatterplot showing the results yielded with MD version at test run 1 (left) and 2 (right) when related to the aggregated results obtained with the PC version. Laterality index, percentage difference between correct LE and RE reports. r_{ICC}, intraclass correlation coefficient. Dot color indicates sex: light blue, females; dark blue, males.

would be predicted. However, the present analyses also revealed a significant difference between the Australian and Norwegian sample when only results of the female participants were compared, indicating that sex alone is insufficient in explaining the difference between the two samples. Based on this observation, Experiment 2 was conducted to further examine the possible effects of language background and sex on the MD results.

EXPERIMENT 2

In the second experiment, data was collected from volunteer users around the world who submitted their test results to a database via the mobile DL application (*iDichotic*). The main aim was to explore if smartphones can produce comparable results in the field as well as in the laboratory and thus be suitable as platforms for large-scale population studies. In particular, we investigated the question of sound language, first as to whether the choice of sound in relation to language background (congruent: Norwegian and English native speakers who also chose their native sound vs. incongruent: participants with various language backgrounds who had to select a non-native sound) influences the results, with implications for the number of native sounds one should provide; and second, as a follow-up to the results of the first experiment, as to whether English and Norwegian syllables selected by native English speakers and native Norwegian speakers, respectively, produce significantly different LIs in this larger sample.

MATERIALS AND METHODS

Participants

The *iDichotic* application was promoted via various media channels (e.g., university news, websites, TV) and word-of-mouth resulting in 508 downloads over the course of 5 months (between release of the application on 11th December 2011 and 11th May 2012). In total, 263 results were submitted (i.e., 52% of those who downloaded the app chose to submit their results). After applying the exclusion criteria, 167 participants were included in the study (see **Table 1** for details). This constitutes the main sample and is the basis for exploring whether the choice of native sound vs. non-native sound has an effect on the results. In addition, a sub-sample of $N = 107$ participants, including only self-reported native speakers of either Norwegian or English who also selected their native language as sound language (see **Table 1**), served as the basis for investigating whether the differences in LIs found between Norwegian and English samples of Experiment 1 also emerge in this larger field data.

Table 1 | Sample characteristics Experiment 2.

		N	Sex		Age (mean ± SD)
			Male	Female	
Stimulus-Language Congruency[a] (analysis 1)	YES	108	69	39	34.1 (±12.6)
	NO	59	38	21	30.5 (±12.2)
	Σ	167	107	60	32.8 (±12.6)
Sound Language[b] (analysis 2)	NOR	78	55	23	32.5 (±11.2)
	ENG	30	14	16	38.3 (±15.1)
	Σ	108	69	39	34.1 (±12.6)

N, number of subjects; SD, standard deviation.

[a]Yes, subject selected native sound; No, subject did not select native sound; Σ, sum.

[b]NOR, Norwegian native speaker that selected Norwegian as sound language; ENG, English native speaker that selected English as sound language.

The following exclusion criteria were applied to the dataset: more than three errors in the identification of homonyms, less than six correct reports, more than 20% hearing asymmetry (deduced from hearing test results implemented in the application, see below), and other-than-first submissions from the same participant, left-handedness, or ambidexterity (self-reported under settings).

Material

The *iDichotic* application (v. 1.1.0) was the same as the pre-release version used in Experiment 1 with some minor graphical and

functional changes concerning the presentation and submission of results.

After downloading and installing the application on their MD, the participants were first directed to the settings page of the application, where they had to select a sound language (Norwegian or English), fill out information about themselves (age, sex, handedness, and native language), as well as perform a hearing test. In this test the loudness of a 1000 Hz tone had to be regulated using a horizontal volume scroll bar to indicate when tone is just inaudible (separate for LE and RE). When these settings were completed, participants could start with the DL task (termed "Listen" test in the application). A pop-up notification reminded the user to wear the earphones in correct ears and check the main volume. Instructions were presented on the screen prompting the user to listen to a series of syllables and report after each trial (by using buttons on the touch screen) the syllable he/she heard best. At completion of the test, which takes approximately 3 min, the results were displayed and the option to submit the data package (see below) to our database was presented.

Data collection

The voluntarily submitted user data package was collected via secure file transfer protocol and stored on the servers at University of Bergen. The data packages were anonymous and included the results, user settings, and submission date, as well as an application-ID (date of application download + random number), which allowed for the exclusion of double submissions. Informed consent was obtained before submission of results by means of a pop-up text window which prompted the user to submit or close.

Statistical analysis

In the main sample, a two-way ANOVA was conducted with LI as the dependent variable (see Experiment 1) and the between-subjects factors of *Sex* and *Stimulus-Language Congruency*. A second two-way ANOVA was conducted in a sub-sample (for sample characteristics, see **Table 1**) with LI as the dependent variable (see Experiment 1) and the between-subject factors *Sex* and *Sound Language*. The level of significance was set to $\alpha = 0.05$ and effect sizes were calculated as η^2 and *d*, respectively. The analysis was performed in PASW 18.0 (IBM SPSS, New York, USA). Power analysis was performed using GPower 3.0 (Faul et al., 2007).

RESULTS

The first ANOVA revealed a significant main effect of *Sex* [$F(1,163) = 4.76$, $p = 0.031$, $\eta^2 = 0.028$] with males having a stronger LI than females (males: $17.6\% \pm 30.8$; females $4.7\% \pm 25.2$). Neither the main effect of *Stimulus-Language Congruency* [$F(1,163) = 0.50$, $p = 0.480$, $\eta^2 = 0.003$] nor the interaction was significant [$F(1,163) = 2.64$, $p = 0.106$, $\eta^2 = 0.015$]. The statistical power of the test for the non-significant main and interaction effect of stimulus-language congruency was with 0.83 sufficiently high to exclude population effect explaining more than 5% of the variance. Finally, a significant intercept [$F(1,163) = 23.02$, $p < 0.001$] indicated a significant REA in the sample (mean LI = $13.0\% \pm 29.5$; $d = 0.44$). Subjects that selected their native sound language displayed a mean LI of $12.5\% \pm 32.5$ compared to $13.8\% \pm 23.2$ of those who did not select their native sound language. Fifty-three out of 59 (89.8%) non-English/non-Norwegian native speakers selected English as the sound language. The distribution of correct RE and LE reports are shown in a scatterplot in **Figure 4**.

In line with the results of the first ANOVA, the second ANOVA revealed a significant main effect of *Sex* [$F(1,104) = 7.03$, $p = 0.009$, $\eta^2 = 0.063$] with males showing a stronger LI than females. Neither the main effect of *Sound Language* [$F(1,104) = 1.20$, $p = 0.277$, $\eta^2 = 0.011$] nor the interaction was significant [$F(1,104) = 0.31$, $p = 0.581$, $\eta^2 = 0.003$]. The statistical power of the test for the main effect of sound language was with 0.80 sufficiently high to exclude population effect explaining more than 7% of the variance. Finally, a significant intercept [$F(1,104) = 6.53$, $p = 0.012$] indicated a significant REA in the sub-sample (mean LI = $12.5\% \pm 32.5$; $d = 0.38$).

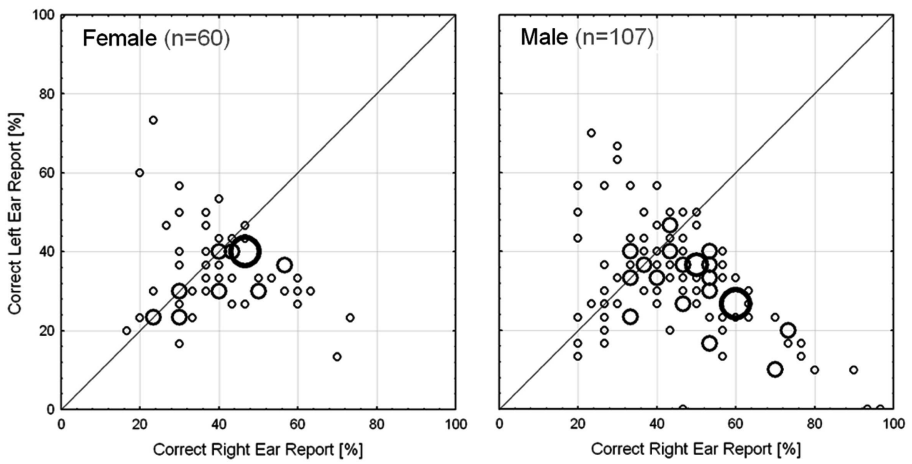


FIGURE 4 | Distribution of the field data separated by sex; collected via *iDichotic*. Size of bubble reflects the number of subjects with the same ear scores (displayed as percentage correct reports of right and left ear stimulus in one test run). Left: female subjects; right: male subjects.

DISCUSSION

Utilizing a MD DL test we collected data in a large international field experiment and were able to replicate the REA usually found with this paradigm (e.g., Studdert-Kennedy and Shankweiler, 1970; Hugdahl and Andersson, 1984), supporting the usability of MDs as "mobile laboratories." Furthermore, we also observed a significant effect of sex, with males displaying a larger REA than females. This finding is in line with a frequently observed stronger behavioral laterality in males (e.g., McGlone, 1980). However, recent meta-analytic evidence (e.g., Voyer, 2011; see also Hiscock et al., 1994) as well as studies utilizing larger study samples (Hirnstein et al., in press), indicate that the sex effect found with DL is rather small, explaining about 1% of the variance in laterality. Against this background, the larger sex effect found in Experiment 2 (2.8% explained variance in the complete sample) is likely due to a sampling bias.

Since large-scale field experiments like this include participants from many backgrounds and not all native sounds can be provided, the question was raised as to whether selecting a non-native sound would have an effect on the ear advantage. This is an important issue because on it depends whether non-natives to a selected sound have to be excluded from the analysis. The results from the first ANOVA showed that also non-native speakers might be included in the analysis, suggesting that lack of non-native materials is not necessarily a hindrance in world-wide data collections.

Based on the findings from Experiment 2, it appears that language background cannot explain the differences observed in Experiment 1, although the same trend toward larger LI in the Norwegian sample compared to the English sample is seen in the present experiment as well as in previous studies (see Discussion of Experiment 1).

GENERAL DISCUSSION

The objective of the experiments reported here was to examine the feasibility of MD applications in laterality research. Having established the validity and reliability of the MD version under controlled conditions in the laboratory (Experiment 1), we examined how the MD application performed in uncontrolled conditions in the field (Experiment 2), where circumstances surrounding self-administration of the test are unknown (e.g., environmental noise, location, headphone quality, subject's state of mind etc.). For example, as seen in an earlier study, background noise can significantly reduce the REA (Dos Santos Sequeira et al., 2010) and thus might also have an effect on the present field data. Despite these issues, the results displayed a significant REA suggesting that laboratory experiments can be replicated in real-life settings via MDs. In addition, the REA appears to be "robust" enough to resist "noise" factors. Thus, the present MD application appears to be a valid and reliable alternative to the traditional method of administering DL on a PC, independent of the experimental setting.

The field experiment results further imply that heterogeneity of a sample should not always be avoided, especially when the aim is to test universal theories of the brain. Other examples for this kind of sampling approach are a study on lexical decisions by Dufau et al. (2011) and another study on mind wandering and mood by Killingsworth and Gilbert (2010), both employing smartphone technology to collect data from users world-wide. Analogous to our experiment, the authors used Apple's App Store for distribution of the application.

The results from both experiments show that although a significant REA was found in all samples, there are also variations between them. The Norwegian sample in Experiment 1 appears to stand out as particularly RE-biased whereas all other samples, including the Norwegian sub-sample in Experiment 2, displayed smaller REAs. This cannot be solely explained by the different sex distributions of the samples, although sex appears to have an effect on speech laterality, as seen in previous studies (e.g., Hirnstein et al., in press; Voyer, 2011; see also Discussion under Experiment 2) as well as in the present Experiment 2. Also language background is not a sufficient factor in explaining the laterality differences observed Experiment 1, since there was no significant effect of sound language in Experiment 2, although previous studies have suggested such a link (see Discussion above). In summary, the variations we see may be due to a combination of factors, that is sex (to a lesser degree) or sound language.

LESSONS FOR FUTURE SMARTPHONE FIELD EXPERIMENTS

Given that environment/background noise can have a significant influence on test results (Dos Santos Sequeira et al., 2010), one should consider collecting data on the circumstances surrounding the testing. For example, the participants could be asked to provide information about their location, or the microphone built into the MD could be used to determine the background noise level. Also data on the hardware (device, headphones) and software version used for the test may be useful information, especially if the test runs on various platforms. One should be aware of systematic errors introduced by different hardware/software, e.g., bias toward one output channel (ear); however, currently, *iDichotic* is limited to Apple's MDs that run iOS software version 5 or later, and we are not aware of any systematic differences between the versions that might have affected our results.

CONCLUSION

Taken together, as here demonstrated regarding the REA in DL, current smartphone technology allows for a validation of laterality phenomena and cognitive constructs in the field. Validation of our mobile application in patients who cannot visit research facilities, for example, hospitalized patients undergoing neuropsychological assessment, is a logical next step. Also, studies designed to investigate longitudinal changes, such as infradian effects of sex hormones like estradiol (e.g., Cowell et al., 2011; Hjelmervik et al., 2012) on laterality, or symptoms-related cognitive fluctuations (e.g., Green et al., 1994; Escandon et al., 2010), as well as molecular genetic studies with the need to recruit large cohorts (e.g., Ocklenburg et al., 2011) could benefit from data collection using MDs.

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APPENDIX

Table A1 | Correct report (mean ± standard deviation) for each sample, test version, and timepoint.

		t1			*t2*		
		LE	**RE**	**LI**	**LE**	**RE**	**LI**
NOR	PC	32.5 (±16.9)	58.0 (±19.4)	27.2 (±38.3)	27.9 (±17.7)	62.0 (±21.8)	36.3 (±41.9)
	MD	28.8 (±16.3)	62.3 (±17.7)	36.5 (±35.3)	25.5 (±12.3)	67.1 (±15.7)	44.2 (±29.3)
AUS	MD	36.2 (±12.3)	44.0 (±14.0)	9.2 (±27.2)	37.6 (±14.0)	48.8 (±15.6)	12.3 (±29.4)

t1/t2, first and second testing, respectively. LE, left ear; RE, right ear; LI, laterality index; NOR, Norwegian sample; AUS, Australian sample.

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How brain asymmetry relates to performance – a large-scale dichotic listening study

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All major mental functions including language, spatial and emotional processing are lateralized but how strongly and to which hemisphere is subject to inter- and intraindividual variation. Relatively little, however, is known about how the degree and direction of lateralization affect how well the functions are carried out, i.e., how lateralization and task performance are related. The present study therefore examined the relationship between lateralization and performance in a dichotic listening task for which we had data available from 1839 participants. In this task, consonant-vowel syllables are presented simultaneously to the left and right ear, such that each ear receives a different syllable. When asked which of the two they heard best, participants typically report more syllables from the right ear, which is a marker of left-hemispheric speech dominance. We calculated the degree of lateralization (based on the difference between correct left and right ear reports) and correlated it with overall response accuracy (left plus right ear reports). In addition, we used reference models to control for statistical interdependency between left and right ear reports. The results revealed a u-shaped relationship between degree of lateralization and overall accuracy: the stronger the left or right ear advantage, the better the overall accuracy. This u-shaped asymmetry-performance relationship consistently emerged in males, females, right-/non-right-handers, and different age groups. Taken together, the present study demonstrates that performance on lateralized language functions depends on how strongly these functions are lateralized. The present study further stresses the importance of controlling for statistical interdependency when examining asymmetry-performance relationships in general.

Keywords: hemispheric asymmetry, lateralization, dichotic listening, task-performance, sex, age, handedness, verbal abilities

INTRODUCTION

Beginning with the discovery of the left-hemispheric dominance of language (Broca, 1861; Dax, 1865) it has now been shown that practically all higher functions including memory, learning, perception, spatial cognition, attention, complex motor skills, and emotion processing show some degree of hemispheric specialization (Hellige, 1993; Davidson and Hugdahl, 1995). At first, lateralization was believed to be a unique human feature (Crow, 2002) but in the meantime it has been documented in a wide range of species (Vallortigara and Rogers, 2005). Brain asymmetries in humans, however, are typically more pronounced than in animals and it has been argued that they gave rise to our superior verbal and intellectual skills (Corballis, 1991, 2009). Previous research has shown that the degree of lateralization in humans is subject to inter- and intraindividual differences. For example, some individuals show strong left-hemispheric language lateralization, others strong-right-hemispheric language lateralization, and still others possess a more bilateral language representation (Knecht et al., 2000). Even within individuals lateralization changes as a function of, for example, sex hormones (Hausmann and Güntürkün, 2000; Bayer and Hausmann, 2009; Hjelmervik et al., 2012) or emotional states (Papousek et al., 2011, 2012). However, not much is known about how degree of lateralization and performance in selected functions are related, which we refer to as the "asymmetry-performance relationship", and the few studies available provide incoherent results. For example, Everts et al. (2009) found that a stronger language lateralization, determined with functional magnetic resonance imaging (fMRI), was correlated with a higher verbal IQ. Chiarello et al. (2009) used visual half-field paradigms to assess language lateralization and also found a positive correlation between the degree of lateralization in these tasks and reading skills. On the other hand, there are also studies showing that performance deteriorates with increasing asymmetry. For example, less lateralized participants outperform more lateralized individuals in a face discrimination task (Ladavas and Umilta, 1983) and when two cognitive tasks (i.e., face discrimination and lexical decision) are performed in parallel (Hirnstein et al., 2008). Moreover, individuals with higher degrees of language lateralization as determined with fMRI (van Ettinger-Veenstra et al., 2010) or magnetic resonance diffusion tensor imaging (Catani et al., 2007) performed

better on tests assessing verbal abilities (van Ettinger-Veenstra et al., 2010) or verbal memory (Catani et al., 2007) than individuals with lower degrees of lateralization. The inconsistent findings are neatly illustrated by Razafimandimby et al. (2011) who found that verb generation correlated both positively with precuneus asymmetry and negatively with cerebellum asymmetry (as determined with fMRI).

Boles et al. (2008) carried out the most extensive investigations regarding the asymmetry-performance relationship. They had data from several visual half-field and dichotic listening (DL) tasks that assessed various verbal and non-verbal cognitive functions. To obtain the asymmetry-performance relationship, they correlated the degree of lateralization derived from these tasks with the overall accuracy (or reaction times) – also derived from these tasks. The results are in line with the inconsistent findings described above. Boles et al. (2008) found positive asymmetry-performance relationships in four tasks assessing auditory linguistic and spatial positional functions. Negative relationships emerged in seven tasks assessing planar categorical, spatial emergent, spatial quantitative, and visual lexical functions. The authors concluded that the asymmetry-performance relationship is function-dependent and suggested a neurodevelopmental model according to which functions that lateralize very early (until 5 years of age) and very late in the ontogenetic development (after 11 years of age) yield positive asymmetry-performance correlations. Functions that lateralize at intermediate stages on the other hand show negative correlations.

The neurodevelopmental theory of Boles et al. (2008) may account for some of the strikingly inconsistent results. However, there are a number of methodological pitfalls which might contribute to the inconsistencies above. One of these issues is the "task purity problem" (Boles and Barth, 2011). If lateralization is assessed with one task and then correlated with performance in another task, correlations between lateralization and performance might be confounded by a third variable and do not reveal the pure asymmetry-performance relationship (Boles and Barth, 2011; but see also the reply of Chiarello et al., 2011). If one derives the performance and lateralization from the same task, however, one is faced with the problem of interdependency between left (L) and right (R) scores. Both the overall accuracy (i.e., sum or mean of L and R) *and* the degree of lateralization [i.e., $(R - L)/(R + L)$ or $(R - L)/(200 - R - L)$] are derived from the same L and R scores. Given that L and R scores are typically correlated with each other, there is a risk that the asymmetry-performance relationship is simply the result of, or at least confounded with, this correlation between L and R scores.

The vast majority of studies that investigated the asymmetry-performance relationship in one task do not address the interdependency issue. To solve this problem, Leask and Crow (1997, 2006) developed a method that compares the asymmetry-performance relationship based on R and L scores with reference models in which R and L scores have been modeled such that they do not correlate. Another advantage of this procedure is that it is data-driven and can detect any form of asymmetry-performance relationships. Most studies simply assume linear asymmetry-performance relationships. By applying the procedure suggested by Leask and Crow (1997, 2006) to data from two visual half-field paradigms (i.e., word recognition, face discrimination), Hirnstein et al. (2010) found an inverted u-shaped association between asymmetry and performance. That is, individuals with a symmetric brain organization performed best and performance deteriorated with increasing left or right lateralization. However, the calculation of the degree of asymmetry $[(R - L)/(R + L)]$ in this study has been criticized by Boles and Barth (2011).

It should be noted that almost all of the aforementioned studies that investigated the asymmetry-performance relationship tested right-handed adults (Catani et al., 2007; Boles et al., 2008; Hirnstein et al., 2010; van Ettinger-Veenstra et al., 2010) leaving it unclear whether the findings also apply to other populations such as left-handers, children and adolescents, which are assumed to be less lateralized in verbal and non-verbal functions (e.g., Rasmussen and Milner, 1977; Everts et al., 2009). In general, interindividual differences in the asymmetry-performance relationship are hardly investigated even though there are hints that they exist. Chiarello et al. (2009) reported that the positive correlation between language lateralization and reading skills was stronger in individuals with a consistent hand preference as compared to participants with an inconsistent hand preference. Hirnstein et al. (2010) found that males with a strong left-hemispheric lateralization in a face discrimination task performed rather poorly, while females with a strong left-hemispheric lateralization performed rather well. Thus the asymmetry-performance relationship might also be sex-specific. Finally, little is known about age effects. Only Barth et al. (2012) studied whether the positive asymmetry-performance relationship that they found in a verbal DL task in adults (Boles et al., 2008) also emerged in children. Moreover, they examined whether, in accordance with their neurodevelopmental model, adults but not children showed a negative relationship in emotional face discrimination. While the results mostly confirmed their hypotheses, some of the correlations did not reach statistical significance. According to the authors this was due to the relatively small sample size (25 children, 32 adults) emphasizing that sufficient statistical power is needed to reveal the asymmetry-performance relationship.

With some exceptions (Boles et al., 2008; van Ettinger-Veenstra et al., 2010; Barth et al., 2012) most of the studies on the asymmetry-performance relationship used visual tasks and visual asymmetry (Ladavas and Umilta, 1983; Boles et al., 2008; Hirnstein et al., 2008, 2010; Chiarello et al., 2009). Since the relationship between brain asymmetry and task performance should be generic and not dependent on sensory modality, similar relationships should be possible to obtain in the auditory modality, using, e.g., a DL task, which is perhaps the most frequently used task for assessing hemispheric asymmetry (see Hugdahl, 2011; Kimura, 2011 for recent overviews of the use of DL in asymmetry research). Over the years, Kenneth Hugdahl and our research group at the University of Bergen have built up a database with DL data, which now comprises 1839 individuals (see Hugdahl, 2003 for a description of the database). The sample covers a wide age range (5–89 years), has a balanced sex ratio (927 females, 912 males) and a proportion of non-right-handers of 8.9% which

is close to the 10% typically observed in the general population (McManus, 2002). The large number of participants allows a comprehensive examination of the asymmetry-performance relationship and further provides an ideal opportunity to also take into account sex, handedness, and age effects. Two previous studies found that overall accuracy in verbal DL increased as asymmetries became stronger (Boles et al., 2008; Barth et al., 2012), however, leaving the interdependency issue of L and R scores unsolved. Using the approach by Boles et al. (2008), the present study examined first whether we could replicate the positive asymmetry-performance relationship found by this group. In a second step, we applied the approach by Leask and Crow (1997, 2006) which controls for the interdependency issues. By applying this approach, we also took sex, handedness, and age into account. In line with Boles et al. (2008), we hypothesized that individuals with stronger ear advantages (corresponding to a stronger degree of language lateralization) would generally report more stimuli correctly. Consequently, non-right-handers, women, and children, who are assumed to be less lateralized for language, should generally report less syllables correctly. However, this requires asymmetry-performance relationships to be consistent across all subsamples.

MATERIALS AND METHODS

PARTICIPANTS

All 1839 participants in the database completed the DL task described below. The database includes data that have been collected by collaborators in many countries, laboratories, and clinics. They all used the same stimulus materials (but in their native language) and procedure for administering the task, specified in a manual prepared by the Bergen group and distributed to collaborators. The database comprises native Norwegian, Swedish, Finnish, English, German, Slovak-, and Spanish speaking individuals. Handedness was assessed with either the Edinburgh Handedness Inventory (Oldfield, 1971) or the Raczkowski questionnaire (Raczkowski et al., 1974). Participants were classified as right- or left-handed, if they preferentially carried out the majority of actions in these questionnaires with the right or left hand, respectively. Seven participants in the database had been coded as ambidexters (0.4%). Since this group was too small for any meaningful statistics, these participants were collapsed with the left-handers into a "non-right-handers" group. When the database was set up many years ago, age was not considered a major variable and participants were only allocated to age groups. Later, the exact age was included additionally. As a result, the exact age is known for 993 participants (54%), but *all* participants had been allocated to one of these groups: children (5–9 years), early adolescents (10–15 years), younger adults (16–49 years), and older adults (≥50 years). The boundary of 16 was chosen as it was, and still is, the lower limit of the Wechsler Adult Intelligence Scale (Wechsler, 2008). The other boundaries were chosen such that the number of participants was fairly balanced in each category by the time the database was set up. In the interest of statistical power we thus used the existing four group system. An overview of the sample with exact numbers of participants across the factors sex, handedness, and age is provided in **Table 1**.

The database comprises participants without known hearing deficits, psychiatric and neurological disorders. The majority of participants had been assessed with a hearing threshold test. All of them were able to detect frequencies of up to 3000 Hz at an intensity of 20 dB and the interaural acuity difference was ≤10 dB.

STIMULUS MATERIAL AND PROCEDURE

The Bergen DL task has been validated as a measure of language lateralization with ^{15}O positron emission tomography (Hugdahl et al., 1999) and the sodium-amytal test (Hugdahl et al., 1997). The task consists of six consonant-vowel syllables (/ba/, /da/, /ga/, /pa/, /ta/, /ka/). For each trial, two syllables are presented at the same time via headphones – one syllable to the left and the other to the right ear. All possible 36 combinations of the six syllables are presented once in a pseudo randomized order, including the six homonyms (e.g., /ba/ /ba/) which were not used in the statistical analysis. The intertrial interval was about 4 s. The syllables are temporally aligned to ensure simultaneous onset of the consonant segment and the mean stimulus duration is around 350–450 ms depending on voice onset time differences between unvoiced and voiced consonants and on the language. The stimuli were presented at a sound intensity of about 70 dB (with slight variations between laboratories and clinics). Again, depending on the laboratory and clinic, stimuli were presented PC-based or via analog or digital tape/CD players. The participants were not informed that there were two different syllables at each trial and their instruction was to report one syllable – the one they heard best and most clearly. Participants were tested with syllables in their respective mother tongue. For instance, native Norwegian speakers completed the task with syllables spoken by a native Norwegian speaker, German participants with syllables spoken by a native German speaker, etc. The syllables were spoken

Table 1 | Number of participants in the Bergen DL database across age, sex, and handedness.

		Children (5–9 years)	Early adolescents (10–15 years)	Younger adults (16–49 years)	Older adults (≥50 years)	Σ
Females	Right-handed	99	208	434	101	842
	Non-right-handed	3	9	68	5	85
Males	Right-handed	100	293	353	88	834
	Non-right-handed	9	24	41	4	78
Σ		211	534	896	198	1839

by a male voice with constant intensity and intonation for all languages. The dependent variable was the number of correctly reported syllables for each ear (maximum correct reports = 30 in total).

DATA ANALYSIS

TRADITIONAL APPROACH Boles et al. (2008)

To compare our data with previous DL findings (Boles et al., 2008), we first used the traditional approach of simply correlating overall accuracy and degree of lateralization. The overall accuracy was determined as the sum of R and L scores, with R and L corresponding to the percentage of correctly reported syllables from the right and left ear, respectively. To determine the degree of lateralization we calculated a laterality coefficient (LC) using the formula $[(R - L)/(R + L)] \times 100$. Positive values thus reflect a right ear/left-hemispheric advantage while negative values correspond to a left ear/right-hemispheric advantage for language perception. This formula was chosen because the Bergen DL Task is a one-response paradigm. That is, in each trial participants report either the left *or* the right ear stimulus depending on which one they perceive best. This is different to two-response paradigms, in which participants are instructed to report all stimuli (i.e., from the left *and* the right ear). In two-response paradigms, accuracy rates for both ears can add to 100% and the mean accuracy across both ears can thus also be 100%. In one-response paradigms, however, only one ear can obtain an accuracy rate of 100% and the mean accuracy can never exceed 50%. Therefore the practice of using two formulas in two-response paradigms (one for mean accuracies above 50% and another for mean accuracies below 50%) does not apply to our paradigm (cf. Repp, 1977).

The overall accuracy and the LC were entered as dependent and independent variables, respectively, in linear and quadratic regressions. Quadratic regressions were computed to test potential u-shaped asymmetry-performance relationships (Leask and Crow, 2006; Hirnstein et al., 2010). Moreover, linear and quadratic regressions were carried out for absolute LC values in order to investigate the relationship between performance and the *strength* of lateralization regardless of direction.

LOESS APPROACH (Leask and Crow, 2006)

The general principle of the alternative approach is to compare the original data with a reference model in which the interdependency has been removed. The procedure is illustrated in **Figure 1**. In **Figure 1A** the overall accuracy was plotted against the LC – both are derived from L and R (i.e., left and right ear accuracy). The regression (red line) was modeled with locally weighted scatterplot smoothing (LOESS), a nonlinear fitting procedure which ascribes a value "*y*" to a given value "*x*" on the basis of (weighted) local "*y*" values (Leask and Crow, 2006). Specifically, we used the Matlab (The MathWorks, Natick, MA, USA) function "rloess" (robust LOESS) with a span of 0.7 (cf. Hirnstein et al., 2010). In a second step (**Figure 1B**) the original data (red line) is plotted against reference models (blue lines) with near to zero correlations between L and R. The reference models were generated from the original data to ensure that the only difference between reference models and original data was the removed L–R-correlation: one side, say L, was displaced by one row such that L from participant 1 was matched with R from participant 2, and L from participant 2 with R from participants 3, etc., until finally L from participant 1839 was matched with R from participant 1. The mean and standard deviation of this displaced L is identical to the original

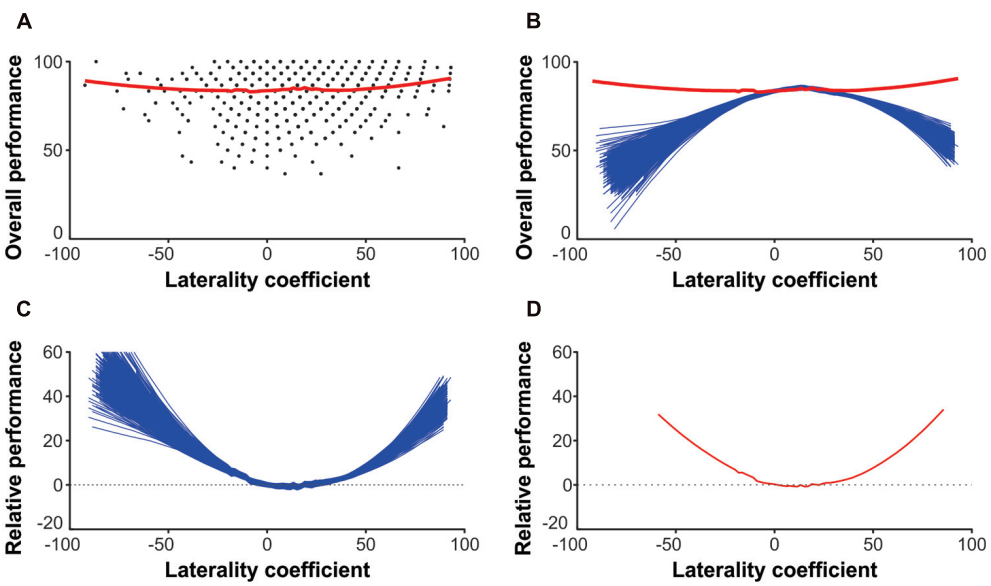


FIGURE 1 | Results and principle of the LOESS method. (A) The raw left and right ear reports are used to compute the laterality coefficient and the overall accuracy. Laterality coefficient and overall accuracy are fitted with LOESS (red line). **(B)** Reference models (blue lines) are computed which are based on the raw left and right ear reports but not correlated ($r < 0.01$). The reference models are also fitted with LOESS. **(C)** The reference models are subtracted **(C)** from the raw data and then averaged **(D)** to reveal the asymmetry-performance relationship controlled for interdependency.

L but the correlation between the displaced L and R is different to the correlation between the original L and R. The displacement was repeated 1838 times leading to 1838 different L–R pairs. As reference models, however, only those L–R pairs were chosen in which the correlation was $r < 0.01$ – thus effectively 0. The overall accuracy and the LC derived from these L–R pairs served as reference models. They were plotted alongside the original data and also modeled with LOESS (**Figure 1B**). To reveal the relationship between degree of lateralization and performance – controlled for interdependency between L and R – all reference models were subtracted from the original data (**Figure 1C**) and averaged to ease interpretation (**Figure 1D**): if the red mean subtraction line is above zero, performance is good – relative to a reference model in which interdependency has been removed. If the line is below zero, then performance is relatively poor and if the line is zero, then no meaningful interpretation of performance is possible. For further details we refer to Leask and Crow (1997, 2006).

RESULTS

To demonstrate that the Bergen DL test shows the expected right ear advantage, left and right ear accuracy rates were subjected to a 2 × 2 × 4 mixed ANOVA with Ear (left, right) as within- and Sex, and Age (children, early adolescents, young adults, old adults) as between-participants factors. Participants reported more syllables from the right (47.0 ± 0.3%) than left ear (33.8 ± 0.3%) as indicated by a significant main effect Ear [$F_{(1,1831)} = 547.99$, $p < 0.001$, partial $\eta^2 = 0.23$]. This right ear advantage became steadily larger with increasing age [interaction Ear by Age $F_{(3,1831)} = 9.64$, $p < 0.001$, partial $\eta^2 = 0.02$], from childhood (right 42.5 ± 0.8%, left 33.7 ± 0.7%) via early adolescence (right 46.6 ± 0.5%, left 35.0 ± 0.5%) and younger adulthood (right 49.9 ± 0.4%, left 35.0 ± 0.4%) to older adulthood (right 48.9 ± 0.9%, left 31.5 ± 0.8%). Bonferroni adjusted *post hoc* tests revealed that compared to children early adolescents reported significantly more syllables from the right ($p < 0.001$) but not the left ear ($p = 1$). Younger adults had an even higher right ear accuracy than early adolescents ($p < 0.001$) but again left ear rates did not differ ($p = 1$). Older adults, however, had a lower left ear rate than younger adults ($p < 0.001$) but the right ear rates did not differ ($p = 1$). In all age groups, the right ear advantage was significant (all $p < 0.001$). The three-way interaction Ear by Sex by Age also became significant [$F_{(3,1831)} = 3.86$, $p = 0.009$, partial $\eta^2 = 0.01$]. *Post hoc* tests revealed that female adolescents reported significantly more syllables from the right ear than female children ($p < 0.01$), while male children/early adolescents did not show such a rise ($p = 1$). The left ear reports did not change in both sexes (all $p = 1$). As a result female early adolescents showed a stronger right ear advantage than male early adolescents, whereas in all other groups males had a numerically stronger right ear advantage than females (see **Figure 2**). The right ear advantage was significant in both sexes in all age groups (all $p < 0.01$).

A main effect of Age [$F_{(3,1831)} = 41.25$, $p < 0.001$, partial $\eta^2 = 0.06$] indicated that younger adults [$M = 42.50\% \pm$ SEM $= 0.2$] generally reported more syllables than older adults (40.2 ± 0.4%), early adolescents (40.8 ± 0.2%), and children (38.1 ± 0.4%). *Post hoc* tests were significant for all comparisons (all $p \leq 0.001$) except for the difference between early adolescents and older adults ($p = 0.993$). The better overall accuracy in younger adults depended upon Sex [interaction Age by Sex with $F_{(3,1831)} = 4.12$, $p = 0.006$, partial $\eta^2 = 0.01$]. While males obtained higher overall accuracy than females in childhood (males 38.5 ± 0.5%, females 37.8 ± 0.5%) and early adolescence (males 41.2 ± 0.3%, females 40.4 ± 0.4%), females reported more syllables correctly than males in younger (females 43.0 ± 0.02%, males 42.0 ± 0.3%) and older adults (females 40.6 ± 0.5%, males 39.7 ± 0.6%). However, none of these sex differences was significant after Bonferroni adjustment (all $p \geq 0.109$).

Handedness was analyzed separately, since there were not sufficient non-right-handers (see **Table 1**) for including this variable in the ANOVA above. Non-right-handers were matched to right-handers on the basis of sex and age. A 2 × 2 ANOVA with Ear and Handedness as within- and between-participants factors, respectively, only revealed a significant main effect Ear

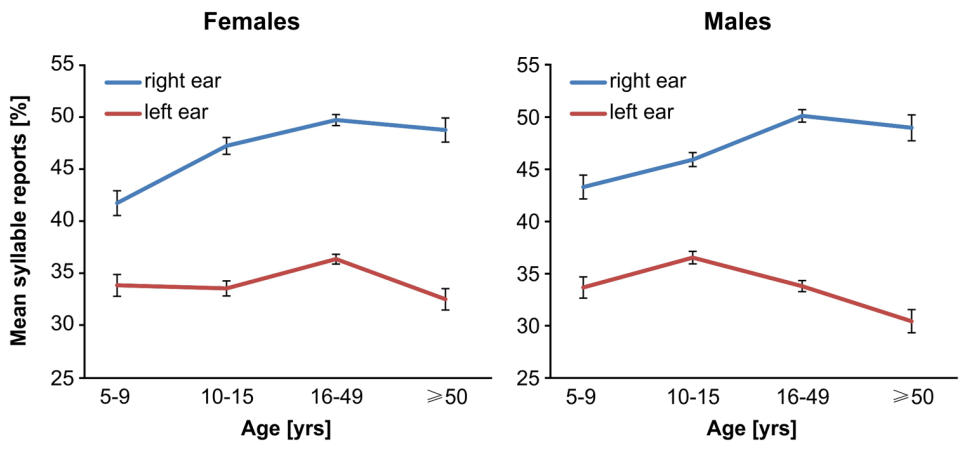


FIGURE 2 | Mean left and right ear reports (±SEM) across sex and age. Both males and females in all age groups report more syllables from the right than the left ear. This right ear advantage is slightly stronger in males than females in all age groups except in early adolescents.

[$F_{(1,324)} = 78.56$, $p < 0.001$, partial $\eta^2 = 0.20$] with the expected right ear advantage (right 46.79 ± 0.7%, left 36.7 ± 0.6%). Neither the main effect Handedness nor the interaction Ear by Handedness reached significance (all $F \leq 1.10$, $p \geq 0.295$).

THE RELATIONSHIP BETWEEN ASYMMETRY AND PERFORMANCE

Traditional approach

A statistically significant, positive correlation emerged between directional LC (preserving the direction of asymmetry) and overall accuracy [$F_{(1,1837)} = 9.21$, $p = 0.002$] showing that participants reported more correct syllables the more strongly their right ear advantage was (**Figure 3**). The correlation coefficient was rather small ($r = 0.07$) and accounted for 0.5% of the variance. The quadratic model also became significant [$F_{(2,1836)} = 5.70$, $p = 0.003$] suggesting that, in general, stronger ear advantage (regardless of its direction) was associated with higher performance. However, the explained variance was only marginally higher than in the linear model ($R^2 = 0.6\%$). The absolute LC and overall accuracy also showed a statistically significant but very small linear correlation ($r = 0.06$, $p = 0.009$) accounting for 0.4% variance. The same applies to the quadratic model [$F_{(2,1836)} = 4.42$, $p = 0.012$, $R^2 = 0.5\%$].

Finally, left and right ear accuracy rates were negatively correlated ($r = -0.51$, $n = 1839$, $p < 0.0001$). Thus higher right ear rates were associated with lower left ear rates.

LOESS approach

Figure 1D shows a u-shaped relationship between asymmetry and performance across all participants. Similar to the traditional approach, the stronger the ear advantage (regardless of its direction) the more syllables were reported correctly. Relative performance declines as the ear advantage becomes smaller and is lowest at an LC of 11.52. **Figure 4** shows the asymmetry-performance relationship for females, males, right- and non-right-handers, children, early adolescents, younger adults, and older adults. The u-shaped curve was similar in all these groups: performance was lowest with a small right ear advantage (i.e., LC between 5 and 15) and steadily improved as the left or right ear advantage became stronger.

DISCUSSION

The present study investigated how the degree of lateralization is related to overall accuracy in a verbal (consonant-vowel) DL task. Previous studies addressing the asymmetry-performance relationship were subject to interdependency issues of L and R scores. Moreover, the large sample size allowed exploring whether the asymmetry-performance relationship varies across sex, age, and handedness.

First of all, the results from the ANOVA confirmed the well-known right ear/left-hemispheric advantage for auditory speech processing (for review Bryden, 1988). This functional asymmetry was dependent upon age and sex, which is discussed in detail in Hirnstein et al. (2013). It should also be noted that the number of participants in the four age groups were different which means that the statistical power to detect effects is higher in early adolescents and younger adults group as compared to children and older adults. Nevertheless, the right ear/left-hemispheric advantage emerged, on average, across all participants and in all subgroups in accordance with the literature (Hugdahl, 2003). However, as can be seen in **Figure 3**, there was considerable interindividual variation with respect to whether a left or right ear advantage emerged and how strong this advantage was. The variability in the degree and direction of the ear advantage in our sample thus allowed us to examine whether DL performance depends on the strength and/or the direction of the ear advantage. The traditional approach of correlating the degree of lateralization with the overall accuracy revealed a significant quadratic model. That is, a u-shaped curve where individuals with stronger right and left ear advantages reported more syllables correctly. However, the explained variance of 0.6% was trivial. Since the bulk of participants had a right ear advantage, the correlation (linear model) also became significant. That is, overall accuracy increased as the right ear advantage increased, but again, the explained variance was low (0.5%) and the correlation coefficient of $r = 0.06$ was well

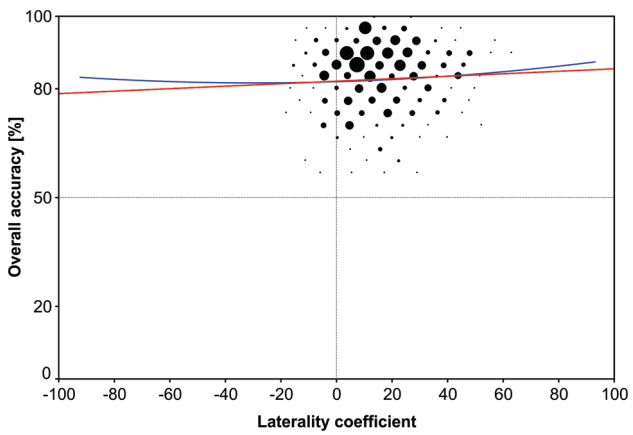


FIGURE 3 | Results of the traditional approach. The bubble chart shows the linear (red line) and quadratic regression (blue line) between overall accuracy and degree of lateralization.

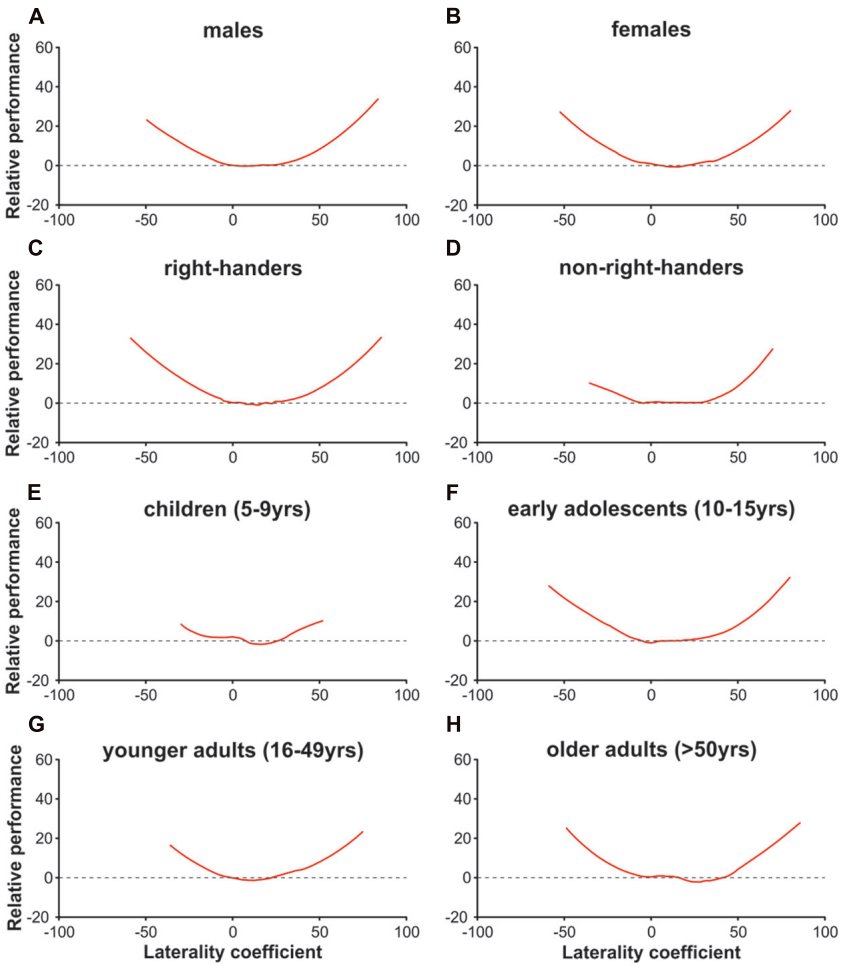


FIGURE 4 | The relationship between (relative) performance and degree of lateralization with the alternative approach in males (A), females (B), right-handers (C), non-right-handers (D), children aged 5–9 (E), early adolescents aged 10–15 (F), younger adults aged 16–49 (G), and older adults aged 50+ (H).

below what is considered a small effect ($r = 0.20$; Cohen, 1988). The flat regression lines in **Figure 3** neatly illustrate how meager the asymmetry-performance relationship is, which merely reached significance because of the large sample size. The LOESS approach (Leask and Crow, 1997, 2006), however, revealed a marked u-shaped relationship across all participants (**Figure 1D**) confirming that stronger ear advantages result in better performance.

This u-shaped relationship was largely in alignment with previous investigations of the asymmetry-performance relationship in verbal DL tasks. Boles et al. (2008) used a consonant-vowel task similar to the Bergen DL task and found a positive correlation between *absolute* ear asymmetry and overall accuracy in right-handed adults. Thus, a stronger ear advantage was associated with higher accuracy, corresponding to the u-shaped curve observed in the present study. The follow-up study by Barth et al. (2012) found only trends for a positive correlation – presumably due to small sample size. For the same reason van Ettinger-Veenstra et al. (2010) might have failed with a sample size of $n = 16$ to find correlations between ear asymmetry and overall accuracy in the non-forced condition of the Bergen DL task.

Why was there such a considerable discrepancy between the traditional and the LOESS approach in the present study? Moreover, why did Boles et al. (2008) find a u-shaped asymmetry-performance relationship (similar to results of the LOESS approach reported here), although they used the traditional approach? The answer to these questions might lie in the response format of the Bergen DL task. As pointed out above, the task in the present study used a one-response paradigm. That is, participants reported *either* the left *or* the right ear stimulus. The advantage of such one-response paradigms is that it deals better with extremely high performances. For example, a participant with 100% overall accuracy could have either reported all stimuli from the left ear, all stimuli from the right ear, or 50% from each ear. Accordingly, the participant would be classified as strongly right-lateralized, left-lateralized or perfectly bilateral. In a two-response paradigm, however, participants with 100% accuracy in both the left and the right ear can only be classified as perfectly

bilateral. Moreover, a one-response paradigm avoids confounding the reports by introducing a working memory component. If more than one answer is required, one syllable has to be kept active in the working memory buffer while the first syllable is reported. The disadvantage with one-response paradigms is that L and R scores are more likely to correlate negatively, increasing the problem of interdependency. In the present study, L and R scores were indeed negatively correlated (r = -0.51, $p < 0.0001$) and therefore the LOESS approach was crucial here. However, this does not mean that the LOESS approach should only be applied to one-response paradigms. It seems reasonable to assume that there are also high (positive) correlations between L and R in two-response paradigms, since participants with high accuracy in one ear/visual half-field typically also perform rather well on the contralateral side. For example, in our own word recognition and face discrimination task we found correlations between L and R scores of $r = 0.60$ ($n = 229$, $p < 0.001$) and $r = 0.55$ ($n = 229$, $p < 0.001$), respectively (Hirnstein et al., 2010). Interdependency issues are thus not limited to one-response paradigms and we therefore suggest employing the LOESS approach whenever substantial correlations between L and R scores arise.

The u-shaped pattern showing higher overall accuracy with increasing ear advantages can be seen – descriptively – in all sex, age, and handedness subgroups (**Figure 4**). Several studies investigated whether right-handers have higher cognitive abilities than, for instance, left-handers (Johnston et al., 2009; Nicholls et al., 2010; Mellet et al., 2013), but only few studies examined whether certain subgroups show a different *relationship* between lateralization and performance. Chiarello et al. (2009) found stronger correlations between verbal lateralization and reading performance in consistent as compared to inconsistent handers, but both groups showed positive correlations. Crow et al. (1998) reported that with increasing manual task asymmetry participants performed better in verbal tasks, but this (again) u-shaped relationship was similar in males and females. In accordance with these findings, the present study suggests that the u-shaped relationship between ear asymmetry and overall accuracy emerged in all subgroups. Although the findings of the present study are of descriptive nature, together with the previous findings it seems that, in general, the relationship between lateralization and performance shows little interindividual variation. Whether these findings can be generalized to other subgroups and non-verbal functions, however, needs to be clarified in future studies. We further hypothesized that groups with, on average, lower degrees of lateralization (females, non-right-handers, children) would, on average, obtain lower overall accuracy. This, however, was not necessarily the case. Indeed, right- and non-right-handers did not show any difference in the magnitude of the right ear advantage and also no difference in the number of reported syllables on average (missing main effect and missing interaction). Moreover, children showed the weakest right ear advantage and the lowest number of reported syllables on average. On the other hand, older adults showed a stronger right ear advantage than younger adults, but reported significantly fewer syllables in general. Likewise, female early adolescents were more strongly lateralized than male early adolescents but reported (non-significantly) fewer syllables in general (for more details Hirnstein et al., 2013).

Why is stronger ear asymmetry associated with higher accuracy? When two consonant-vowel stimuli are presented simultaneously, as in the present study, participants sometimes experience sound fusion, which makes it very difficult to correctly report stimuli. For instance, /ba/ and /ta/ are often merged into the sounds /pa/ or /da/ (Repp, 1977). In participants with a clear left or right ear preference, the signal strength for stimuli from the dominant ear seems to be consistently higher than for the non-dominant ear. As a result such fusions are less likely to occur and the error rate might be lower compared to participants without a clear ear preference where the signal from both ears is about equally strong (cf. Hirnstein, 2011). Although speculative at this stage, a reduced risk of such dichotic fusion errors in participants with a clear ear asymmetry might provide a reasonable explanation for the observed u-shaped curve. This also explains why asymmetry-performance relationships reported for verbal DL cannot be necessarily extrapolated to other tasks, processes, and sensory modalities, and thus might partly explain inconsistencies between studies, regardless whether the traditional or LOESS approach is used. For example, Hirnstein et al. (2010) found an *inverted* u-shaped relationship between degree of lateralization and accuracy in verbal and non-verbal visual half-field paradigms (i.e., word recognition and face discrimination). In this study, overall performance deteriorated as participants became more strongly lateralized. Thus, despite our expectation that asymmetry-performance relationship should not be different between sensory modalities, there may be different processes operated in visual as compared to auditory laterality tasks.

Several implications can be derived from previous studies together with the present findings. First, asymmetry-performance relationships are indeed task-dependent (Boles et al., 2008). As far as language is concerned, however, stronger lateralization seems to be associated with better performance in verbal abilities (Catani et al., 2007; Boles et al., 2008; Chiarello et al., 2009; Everts et al., 2009; van Ettinger-Veenstra et al., 2010; Barth et al., 2012). Second, the assumption that stronger brain asymmetry is generally beneficial, which has been reported especially in the animal literature (Güntürkün et al., 2000; Rogers et al., 2004), is not correct *per se*. As pointed out by Corballis (2005, 2006), both strong asymmetries as well as a more bilateral functional brain organization have advantages and disadvantages which need to be held in balance. Finally, the u-shaped (or inverted u-shaped) curves reported so far (Leask and Crow, 2006; Boles et al., 2008; Hirnstein et al., 2010) have their midpoints close to a lateralization degree of zero. Thus, participants with left- and right-hemispheric lateralization essentially show the same pattern: stronger asymmetry leads to better (or poorer) performance. This implies that *degree* of lateralization is far more important for performance than *direction* (i.e., whether a function is lateralized to the left or right hemisphere).

CONCLUSION

Taken together, the findings of the present study showed that participants with stronger left or right ear advantage had higher overall accuracy in the verbal DL task. This u-shaped relationship between asymmetry and performance was similar across sex, age, and handedness and might result from fewer dichotic fusion errors

in participants with clear ear asymmetries. In line with previous findings, the present study suggests that the degree of functional cerebral asymmetry is associated with the level of performance of a corresponding task. The hemisphere to which a function is lateralized, however, does not appear to be crucial. On the other hand, whether an asymmetric or symmetric brain organization is beneficial for performance depends on the particular task and the mental process(es) involved. Finally, the present study also emphasizes the importance of controlling for statistical interdependency between L and R scores when examining the asymmetry-performance relationship, particularly in one-response paradigms.

AUTHOR CONTRIBUTIONS

Marco Hirnstein carried out the analyses. All authors contributed to the conception of the present study and participated in drafting the article.

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GENERAL COMMENTARY
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Erratum: How brain asymmetry relates to performance – a large-scale dichotic listening study

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Keywords: hemispheric asymmetry, lateralization, dichotic listening, task-performance, sex, age, handedness, verbal abilities

An erratum on

How brain asymmetry relates to performance – a large-scale dichotic listening study
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On page 1 the final sentence in the second column should read: "Moreover, individuals with *lower* degrees of language lateralization as determined with fMRI (van Ettinger-Veenstra et al., 2010) or magnetic resonance diffusion tensor imaging (Catani et al., 2007) performed better on tests assessing verbal abilities (van Ettinger-Veenstra et al., 2010) or verbal memory (Catani et al., 2007) than individuals with *higher* degrees of lateralization."

On page 7 the final sentence of the first column should read: "For the same reason van Ettinger-Veenstra et al. (2010) might have failed with a sample size of $n = 16$ to find correlations between ear asymmetry and *behavioral language tests* in the non-forced condition of the Bergen DL task."

On page 8 the final paragraph of the discussion should read: "As far as language is concerned, however, stronger lateralization seems to be associated with better performance in verbal abilities (Boles et al., 2008; Chiarello et al., 2009; Everts et al., 2009; Barth et al., 2012, *but see* Catani et al., 2007; van Ettinger-Veenstra et al., 2010)."

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The cortical microstructural basis of lateralized cognition: a review

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The presence of asymmetry in the human cerebral hemispheres is detectable at both the macroscopic and microscopic scales. The horizontal expansion of cortical surface during development (within individual brains), and across evolutionary time (between species), is largely due to the proliferation and spacing of the microscopic vertical columns of cells that form the cortex. In the asymmetric planum temporale (PT), minicolumn width asymmetry is associated with surface area asymmetry. Although the human minicolumn asymmetry is not large, it is estimated to account for a surface area asymmetry of approximately 9% of the region's size. Critically, this asymmetry of minicolumns is absent in the equivalent areas of the brains of other apes. The left-hemisphere dominance for processing speech is thought to depend, partly, on a bias for higher resolution processing across widely spaced minicolumns with less overlapping dendritic fields, whereas dense minicolumn spacing in the right hemisphere is associated with more overlapping, lower resolution, holistic processing. This concept refines the simple notion that a larger brain area is associated with dominance for a function and offers an alternative explanation associated with "processing type." This account is mechanistic in the sense that it offers a mechanism whereby asymmetrical components of structure are related to specific functional biases yielding testable predictions, rather than the generalization that "bigger is better" for any given function. Face processing provides a test case – it is the opposite of language, being dominant in the right hemisphere. Consistent with the bias for holistic, configural processing of faces, the minicolumns in the right-hemisphere fusiform gyrus are thinner than in the left hemisphere, which is associated with featural processing. Again, this asymmetry is not found in chimpanzees. The difference between hemispheres may also be seen in terms of processing speed, facilitated by asymmetric myelination of white matter tracts (Anderson et al., 1999 found that axons of the left posterior superior temporal lobe were more thickly myelinated). By cross-referencing the differences between the active fields of the two hemispheres, via tracts such as the corpus callosum, the relationship of local features to global features may be encoded. The emergent hierarchy of features within features is a recursive structure that may functionally contribute to generativity – the ability to perceive and express layers of structure and their relations to each other. The inference is that recursive generativity, an essential component of language, reflects an interaction between processing biases that may be traceable in the microstructure of the cerebral cortex. Minicolumn organization in the PT and the prefrontal cortex has been found to correlate with cognitive scores in humans. Altered minicolumn organization is also observed in neuropsychiatric disorders including autism and schizophrenia. Indeed, altered interhemispheric connections correlated with minicolumn asymmetry in schizophrenia may relate to language-processing anomalies that occur in the disorder. Schizophrenia is associated with over-interpretation of word meaning at the semantic level and over-interpretation of relevance at the level of pragmatic competence, whereas autism is associated with overly literal interpretation of word meaning and under-interpretation of social relevance at the pragmatic level. Both appear to emerge from a disruption of the ability to interpret layers of meaning and their relations to each other. This may be a consequence of disequilibrium in the processing of local and global features related to disorganization of minicolumnar units of processing.

Keywords: minicolumn, cytoarchitecture, lateralization, asymmetry, face-processing, language, schizophrenia, autism

The significance of human brain asymmetry depends broadly on two lines of evidence: the presence of anatomical asymmetries at the large and small scale and the presence of functional lateralization of cognitive functions, most notably language. A major challenge is that the nature of the link between the two is not clear. For example, the simplest models tend to be based on the principle that a larger brain region on one side of the brain denotes dominance for a lateralized function (Galaburda, 1995). However, there are frequently exceptions to this rule. Asymmetries vary by degree between individuals. Furthermore, the correspondences between structures within the same individual and between structural asymmetry and functional lateralization are often inconsistent.

AUDITORY CORTEX, LANGUAGE, AND ASYMMETRY

In humans, the superior temporal gyrus (STG) contains perhaps the most prominently asymmetrical brain area: the auditory association cortex of the planum temporale (PT), lying posterior and lateral to Heschl's gyrus, contributing to the hemispheric asymmetry of the posterior Sylvian fissure. This region plays a key role in phonological processing and forms part of the receptive language region often identified as Wernicke's area. Geschwind and Levitsky (1968) found leftward asymmetry (greater size on the left than the right) of the PT in two-thirds of individuals. Around the same time in the late 1960s, Juhn Wada's test of alternately anesthetizing the cerebral hemispheres had also demonstrated the widespread left-hemisphere dominance for language processing. The implied association between leftward structural asymmetry and functional lateralization led some authors to suggest that cerebral asymmetry is a defining feature of the human brain (Corballis, 1991; Crow, 2000). In fact, there is uncertainty concerning the relationships between different measures of asymmetry and corresponding language lateralization. Individuals with situs inversus (reversal of the bodily organs) who have reversed frontal petalia (asymmetric extension of the anterior limit of the frontal lobe) still show normal asymmetry of the PT (Kennedy et al., 1999). This suggests dissociation between elements of asymmetric structure. Other researchers have found that, although PT asymmetry and language laterality are significantly left-hemisphere biased, they may not be correlated (Eckert et al., 2006).

A more complex picture has emerged from psychological and neuroimaging studies which have clarified more precise associations between structure and function. The PT may be subdivided into medial, lateral, and caudal parts, each associated with different aspects of speech processing (Tremblay et al., 2013). Anterior STG is sensitive to syntactic word category violation in a sentence (Friederici et al., 1993), while the posterior STG supports a left-hemisphere bias for phonological processing (e.g., Robson et al., 2012). Meanwhile, the right-hemisphere auditory areas are dominant for music perception in untrained listeners (Ono et al., 2011), although this functional asymmetry is modulated by degrees of expertise and ability. Therefore, the evidence for two aspects of lateralization, structural and functional, has become increasingly refined, suggesting that lateralized functions (e.g., language) often depend on multiple cognitive components (e.g., phonology, prosodic intonation etc.) that may be modular in nature and structural asymmetry (e.g., Sylvian fissure length) depends on smaller structural components (e.g., anterior, posterior STG, sub-regions of PT). The relationship between structure and function appears to depend on the lateralization of these localized components.

The search for the link between structure and function leads therefore to the small-scale modular components that constitute the functions of interest. Indeed, inconsistent matching between measures of asymmetry and lateralization may be due to attempts to match incompatible levels (e.g., attempting to match a small structural subregion asymmetry with the lateralization of a function that emerges from the interaction of multiple regions). In terms of function, two underlying processing biases are apparent at a basic level that may contribute to language laterality. First, the left hemisphere is biased toward processing short temporal transitions in the sound signal which is especially suitable for recognizing speech (Efron, 1963; Tallal et al., 1993; Shtyrov et al., 2000; Zatorre et al., 2002). Conversely, the right hemisphere is biased for spectral sound processing (Zatorre and Belin, 2001) which may form the basis of the dominance of music perception in the right hemisphere in untrained listeners. Second, evidence supports the concept that in the generation of "meaning" the left parieto-occipito-temporal junction (Wernicke's area) is associated with the activation of more discrete, narrow, semantic associations, whereas the right hemisphere activates more distributed semantic fields appropriate to its greater sensitivity to context (Rodel et al., 1992). Event-related potentials (ERPs) in the STG are the first to diverge depending on the semantic categories of words (Dehaene, 1995) consistent with a role for this region early in category discrimination (although see Eckert et al., 2006 for consideration of an alternative – that this is a response to phonology secondary to meaning). Such ERPs are asymmetrical between the hemispheres, for example, a left temporo-parietal negativity for animal names and verbs and a left inferior temporal negativity for proper names.

What level of structural focus is appropriate to identify corresponding anatomical components underlying regional asymmetry? Not all measures of the superior temporal plane identify hemispheric asymmetries. Since the original observations by Geschwind and Levitsky (1968), Zetzsche et al. (2001) have shown that the definition of PT borders influences the detection of cerebral asymmetry. Pearlson et al. (1997) suggested that measurement of surface area is more important than volume and Barta et al. (1997) detected asymmetries by surface area measurements that were not detected by volume measures. Both are consistent with the hypothesis of Harasty et al. (2003) that asymmetry of the PT is due to lengthening of the cortex on the left side relative to the right. These measures at the surface may therefore indirectly reveal differences in the underlying neural circuitry that is the basis for differences in processing bias between the hemispheres.

The horizontal expansion of cortical surface during development (within individual brains), and across evolutionary time (between species), is largely due to the proliferation and spacing of radial minicolumns of cells that form the cortex (Rakic, 1995). These microscopic structures persist throughout the mature brain, where they span the 3–4 mm depth of the cortex with a horizontal width of approximately 50 μm. Minicolumns emerge by radial migration of cells toward the brain's surface during embryonic formation of the cerebral cortex. Column-like radial

organization is found for cell bodies and their axonal and dendritic connections. Auditory cortex in the STG develops a clear columnar cell distribution by the third trimester of fetal life, which is established in early childhood, although axonal maturation continues up to at least 12 years of age (Moore and Guan, 2001) and probably later in more associative regions. Although the human minicolumn asymmetry is not large (Buxhoeveden et al., 2001; Hutsler, 2003), it is estimated to account for a surface area asymmetry of 8–9% of the region's size (Chance et al., 2006). Notably, this asymmetry of minicolumn spacing is absent in the equivalent areas of the brains of other apes (Buxhoeveden et al., 2001). The microscopic asymmetry in humans is also detected at the slightly larger scale of inter-connected "macrocolumn" patches (approximately 500 μm diameter) which are more widely spaced in the left than in the right auditory association cortex (Galuske et al., 2000). Recent single-unit electrophysiological recordings have demonstrated that cells within the same minicolumn share greater similarity of stimulus sensitivity than with cells in neighboring columns (Opris et al., 2012). The combination of stimulus-sensitive columns in a region presumably confers processing specialization.

Minicolumn organization in the PT has been found to correlate with cognitive scores (tests such as the Mini Mental State Exam which covers a range of tasks including object naming and simple sentence construction; Chance et al., 2011b). The relationship with cognition was specific to minicolumn measures and was not found for neuron density, as also reported in monkeys (Cruz et al., 2009). It has been suggested that greater spacing of minicolumns in human association cortex results in less-overlapping dendritic trees and allows more independent minicolumn function (Seldon, 1981a,b). This is consistent with the association between the greater surface area and the wider spacing of evoked electrophysiological activity peaks in the superior temporal plane of the left hemisphere compared with the right (Yvert et al., 2001). Harasty et al. (2003) have developed the notion that widely spaced minicolumns function as discrete units facilitating computational processing of more independent components, whereas densely spaced minicolumns permit greater overlapping co-activation and therefore confer more holistic processing. In Jung-Beeman's (2005) model, the basal dendrites of right-hemisphere pyramidal neurons have longer initial branches and more synapses further from the soma than left-hemisphere neurons where the more widely spaced minicolumns have more dendritic branching within their territory. Wider minicolumn spacing is therefore associated with higher resolution processing across less-overlapping basal dendritic fields whereas dense minicolumn spacing is associated with lower resolution, holistic processing due to relatively greater distal sampling of more overlapping fields (Jung-Beeman, 2005).

EVOLUTIONARY COMPARISON OF AUDITORY AND FACE-PROCESSING ASYMMETRIES

It has been suggested by some (Annett, 1985; McManus, 1985) that hemispheric asymmetries are human specific and offer a neural correlate of uniquely lateralized function, including language, in humans. A challenge to this thesis is found in comparative neuroanatomical studies that have reported the presence of asymmetries in other primate species (LeMay and Geschwind, 1975; Holloway and De La Coste-Lareymondie, 1982; Gannon et al., 1998). However, in contrast with the macroscopic picture based on surface landmarks, current evidence indicates evolutionary discontinuity for microscopic, cytoarchitectural asymmetry. Region size estimates based on cytoarchitecturally defined boundaries have found that asymmetries are weaker in chimpanzees compared to humans (Spocter et al., 2010), indicating that species differences in asymmetry are more readily identified when cytoarchitectural features are used. Hemispheric asymmetries at the neuronal level show yet more consistent differences between humans and other primates (Chance and Crow, 2007). Asymmetry in the spacing of minicolumnar units of neurons in the human PT is absent in the brains of other primates (Buxhoeveden et al., 2001), and there is a preponderance of large layer III pyramidal neurons (Hutsler, 2003) with wider dendritic arbors (Seldon, 1981a,b) filling the space in the left hemisphere compared with the right in humans. Both Broca's area and Wernicke's area in humans have hemispheric asymmetries of neuropil (Amunts et al., 1999; Anderson et al., 1999). Chimpanzees lack neuropil asymmetry in the equivalent areas (Sherwood et al., 2007). Neuron density in the posterior STG (area Tpt) in chimpanzees is not asymmetrical (Schenker et al., 2005). It is worth acknowledging, however, that symmetry of cytoarchitectural organization may not always be detected – Spocter et al. (2012) did not detect a significant asymmetry of neuropil fraction in the PT or Heschl's gyrus in chimpanzees or humans.

Face processing is another highly evolved ability in primates that provides an interesting comparison in two respects – it is asymmetrically dominant in the opposite direction to language, i.e., face processing is dominant in the right hemisphere in humans (Kanwisher et al., 1997), and it is also a function successfully performed by our closest primate relative, the chimpanzee (Parr et al., 2009). Although both species perceive faces in a predominantly holistic manner (see Taubert and Parr, 2010), this process is clearly lateralized in humans in whom holistic analysis is biased to the right hemisphere (while individual facial features are detected in the left hemisphere; Rossion et al., 2000). The face processing area in the ventral temporal cortex is part of the brain network supporting social cognition in humans and other primates and is found in the mid-fusiform region (roughly equivalent to Brodmann area 37 in human brain). This area falls within a larger surrounding region that processes visual objects in general. This local specialization and the high heritability of face processing (Zhu et al., 2010) make it plausible that there is a detectable neuroanatomical correlate in this region, although the extent to which the neural structure depends on genetic contribution or early social learning is unresolved.

In humans, cells have become large and less densely packed in the evolution of mid-fusiform cortex compared to the chimpanzee and this is accentuated in the left hemisphere with the result that there is an inter-hemispheric asymmetry that is not found in chimpanzees (Chance et al., 2013). Consequently, in humans, the wider minicolumns and larger neurons are found in the hemisphere opposite to the one that is dominant for face perception. Therefore, unlike auditory language processing, it

appears that the arrangement of minicolumns that confers dominance for face processing is the thinner, denser spacing that is found in the right hemisphere (Chance et al., 2013). Meanwhile, the absence of asymmetry in chimpanzees may relate to better performance than humans in tasks such as inverted face recognition that have ecological validity for chimpanzees (Matsuzawa, 2007). The human asymmetry is relatively confined to the mid-posterior fusiform region, as a previous study that included the more anterior fusiform (area 20) reported that minicolumn width in human subjects did not show a statistically significant asymmetry (Di Rosa et al., 2009). A further indication that this functional specialization is associated with minicolumn structure – face discrimination ability is reduced in old age (an effect described as "dedifferentiation"; Goh et al., 2010) and marked minicolumn alteration is also found in fusiform cortex in old age (Di Rosa et al., 2009). As with auditory language processing, there is also left-hemisphere dominance for written language and disordered reading is associated with damage to the left temporo-parietal area (the angular gyrus), first noted by the 19th-century neurologist Dejerine. However, inability to read ("pure alexia") is associated with damage to the left mid-fusiform gyrus (Leff et al., 2006). It has been suggested that the wider minicolumn spacing in this region of the left hemisphere may relate to its role in visual word recognition in humans in addition to its role in face processing (Chance et al., 2013).

MECHANISTIC MODELS

If the point of convergence between functional and anatomical lines of evidence implicates these small, modular units, a mechanistic model is desirable to explain this across different domains of processing. In the visual domain, it is possible that wider minicolumn spacing may be associated with detailed feature processing, whereas thin minicolumns may facilitate holistic, configural processing of the type usually associated with face processing. In such a scheme, face processing is similar to music processing. Holistic, configural processing for face recognition (or music) benefits from the computational overlap generated by densely spaced minicolumns in the fusiform gyrus. This mechanistic interpretation is consistent with a correspondence between the rightward lateralization of holistic face processing and the thin minicolumns found in the right hemisphere in humans and replicates the structure–function correspondence found in the auditory domain although the processing demands of the function lead to different hemispheric dominance. This suggests that minicolumn width is dissociated from "dominance," *per se*, and instead relates to the type of processing: featural or holistic. The wider minicolumn spacing in the left STG facilitates fine temporal discrimination because minicolumns function as more discrete computational elements, whereas dense minicolumn spacing in the right STG supports broad spectral processing, due to the minicolumns' greater computational overlap. The hemispheric processing bias for a given task is likely to depend on the degree to which task success emphasizes local or global processing and the hemispheric asymmetry of minicolumnar units in the brain region associated with that functional domain. This concept refines the simple notion that a larger brain area is associated with dominance for a function and offers an alternative, mechanistic explanation associated with "processing type" (Van Veluw et al., 2012).

The processing-type hypothesis has the advantage of acknowledging the active role of the "non-dominant" hemisphere. It is recognized increasingly that many tasks combine elements of both holistic and featural processing (Rossion et al., 2000). Thus, two streams of processing occur in parallel – global processing in broad-activation fields of the right hemisphere and local processing in focused fields of the left hemisphere. In isolation, these streams simply encode two separate levels of detail, but by cross-referencing the differences between the active fields of the two hemispheres via the corpus callosum the relationship of local features to global features may be encoded. The emergent hierarchy of features within features is a recursive structure that may functionally contribute to generativity – the ability to perceive and express layers of structure and their relations to each other. It has been argued that recursive generativity is an essential, or even, the key component of human language behavior (Crow, 2005). The description here is consistent with such a scenario although it cannot be concluded that the presence of recursion necessarily entails this form of structural asymmetry. Cytoarchitectural asymmetries have been found in normal auditory cortex that correlate with the number of axons passing through the connecting regions of the corpus callosum (Chance et al., 2006). A greater number of minicolumnar units in the hemispheric region that is typically functionally dominant was associated with more interhemispheric connections through the area of the corpus callosum connected to that region.

This mechanistic, processing-type hypothesis potentially contributes to a coherent, descriptive account of cerebral asymmetries of structure and function. However, it is also necessary to identify an evolutionary advantage conferred by this organization, particularly if it is different in humans from other apes. Although not originally associated with asymmetry, Gabora (2002) has proposed a model of the evolutionary enhancement of cognitive processing capacity in humans through the cross-referencing of different levels of conceptual organization. Similar to the recursive process described above, Gabora (2002) describes the interpolation between concepts at "varying levels of abstraction (i.e., cup, container, thing)" as providing stepping stones in a recursive process of "variable focus," She speculates that a pre-palaeolithic mind "activated regions of conceptual space of fixed size with limited ability to focus," but the capacity for variable focus evolved enabling alternately widening and narrowing the "activation function." Although Gabora (2002) describes this as a process of focus fluctuating over time, at least part of this requirement may be met concurrently by the asymmetry between hemispheres as they process different levels of abstraction. Furthermore, although Gabora's (2002) "activation function" was not clearly defined, it seems reasonable to interpret it not just in the abstract but as a field of activated units such as the overlapping minicolumns described above.

PSYCHOLOGICAL SPACE AND LATERALIZED PROCESSING

The Gabora's (2002) model suggests an evolutionary benefit that may be provided by different levels of processing, compatible with existing lateralized processing biases. The proposed advantage of

variable focus is to expand the capacity of conceptual space by interpolation between concepts. In statistical terms, it is equivalent to the generation of continuous data rather than categorical data. In psychological terms, it may be described as the contrast between dimensional and categorical processing. Therefore, if the mechanistic interpretation of microstructural asymmetries is related to this interpolation between concepts and therefore to the generation of continuous dimensions that define a continuous conceptual space, one would expect some association with the organization of the dimensions of conceptual space in the two cerebral hemispheres.

It is often challenging to obtain data for the separate hemispheres, however, in the language domain some investigations have provided data on the organization of semantic space in each hemisphere. Taylor et al. (1999) found that the right hemisphere uses more dimensions than the left hemisphere to represent the semantic map in typical subjects. It is unclear if more dimensions constitutes less efficient coding (i.e., in the right hemisphere each dimension may contribute less to the representation of different concepts, whereas in the left hemisphere the dimensions are more discriminatory and so fewer are needed) or more complex representation (i.e., the right hemisphere may take account of more aspects of a given concept). However, more diffuse activation of the network in response to a linguistic stimulus, consistent with the model of holistic, overlapping activation described above, has been proposed to explain the lesser discrimination between primary and secondary word meanings that is also typically found in the right hemisphere (Weisbrod et al., 1998). This lower resolution discriminative capacity in the right hemisphere is found for face processing even as the right hemisphere is also dominant for making categorical (face vs non-face) distinctions (Meng et al., 2012). This is consistent with the notion that the holistic processing of the densely spaced minicolumns in the right hemisphere facilitates broad categorical processing, whereas the left hemisphere differentiates components within dimensional psychological space. The combination of an increased number of dimensions and more diffuse activation in the right-hemisphere network suggests that the dimensions are partly correlated and less separable than truly orthogonal dimensions.

The phenomenon of key dimensions along which concepts can be organized provides a structure for mentally sorting concepts. This is desirable so that semantic information may be efficiently processed at different levels of elaboration (Craik and Lockhart, 1972). Similar to Gabora's (2002) variable focus, a benefit may be conferred by complementary forms of elaboration with one hemisphere emphasizing the clear separation of concepts and the other allowing more overlap. Different metrics underlying the conceptual space are possible (Gardenfors, 2000), which suggest differences in conceptual organization corresponding to hemisphere differences. Just as with the revolution in understanding of the physical universe in the early 20th century, which indicated that physical space is curved, there have been suggestions that the underlying structure of conceptual space is also not what we may first assume. For example, various psychological spaces are better represented by the "city-block" metric (Arabie, 1991) rather than the familiar Euclidean metric that has been typically assumed (e.g., in multi-dimensional scaling analysis such as Paulsen et al., 1996). The metric is so-called because the distance between concepts is measured as if restricted to a grid-like system of roads (hence "city-block" or "Manhattan" metric) rather than "as the crow flies" in Euclidean space. In the city-block metric, points equidistant from a central point lie on a square around it rather than a Euclidean circle. It has been argued that the sharp-cornered form of the non-Euclidean city-block metric better models the natural tendency to perceive discontinuities between concepts with the corners of a square creating a discontinuity between the concepts on either side of them (Arabie, 1991; Gardenfors, 2000). The orthogonal edges of the square mimic the way conceptual dimensions (such as "size" and "domesticity") are not arbitrary and interchangeable. The difference between hemispheres in the separation and correlation between dimensions suggests a hemispheric difference in the metric of the conceptual space.

The separation of conceptual dimensions also changes during development. Normally, a developmental shift occurs: whereas older children and adults perceive dimensions such as high and tall, or big and bright, to be separable, young children tend to confuse these concepts (Carey, 1978). Goldstone and Barsalou (1998) have described the development of reasoning about dimensions: "dimensions that are easily separated by adults, such as the brightness and size of a square, are treated as fused together for children. . . [they] have difficulty identifying whether two objects differ on their brightness or size even though they can easily see that they differ in some way. Both differentiation and dimensionalization occur throughout one's lifetime." This has been described as a developmental shift from a more Euclidean cognitive metric to the more separable dimensions of the city-block metric (Gardenfors, 2000). The development of more orthogonal dimensions therefore is associated with more sophisticated cognitive discriminative ability. Aspects of brain structural maturation and plasticity presumably relate to this process of cognitive maturation. The increase in discrimination associated with orthogonal dimensions is similar to the acquisition of expertise, which is often associated with left-hemisphere specialization for fine-grained difference judgements, e.g., for faces, word meaning and music. The process, extended over childhood, is also likely to be influenced by the social and cultural environment, including the requirements of social integration and communicative pressure for shared conceptual frameworks. Appropriately, it is the same hemisphere (the left) that is associated with the acquisition of expert discrimination and dominance for the communicative faculty of language that reinforces it.

SCHIZOPHRENIA AND AUTISM

Testing the mechanistic role of cytoarchitectural asymmetry on these aspects of cognitive function is challenging as the lateralized functions of interest appear to be confined to humans and, debatably, few other animals. However, disruptions of both minicolumnar structural organization and lateralized function are found in human neuropsychiatric disorders which provide further insight.

Altered cerebral asymmetry has been found in schizophrenia (Bilder et al., 1994; DeLisi et al., 1997; Chance et al., 2005) and the prominent role of language anomalies in schizophrenia also implicates lateralization (Crow, 1990). The auditory region offers one

of the clearest associations between psychotic symptoms and brain structure, as it is activated during auditory hallucinations (Shergill et al., 2000; Ropohl et al., 2004). The loss of left-hemisphere ERP mismatch responses to anomalous words at the end of a sentence, based on incongruous word meaning (Spironelli et al., 2008), provides a link between the sensory, phonological abnormalities and linguistic meaning. Reduced gray matter in this area, including the PT, is one of the most replicated structural changes in the disorder. Minicolumn asymmetry of this region is also altered in male patients (in whom illness is usually more severe) in such a way that both hemispheres are configured more like the typical right hemisphere (Chance et al., 2008).

Word generation (semantic fluency) tests the integrity of the semantic network that encodes basic knowledge about the meanings of words. Patients with schizophrenia have been shown to have networks that are less organized than those of control subjects (Paulsen et al., 1996; Rossell et al., 1999). If increased number of dimensions is taken to be indicative of more diffuse activation in the right-hemisphere network in normal subjects (as described above; Taylor et al., 1999), then the hypothesis that patients have unusually diffuse semantic associations in the left hemisphere as well as the right hemisphere (Weisbrod et al., 1998) predicts that patients use more, poorly discriminative dimensions overall. This is supported by several studies which reported less effective mapping of semantic space in low dimensions for schizophrenia, indicating the requirement for more dimensions (Paulsen et al., 1996; Rossell et al., 1999). The evidence that semantic category boundaries are less clear in schizophrenia (Paulsen et al., 1996) raises the prospect that the city-block metric may not provide a better fit for patients. In adolescent onset schizophrenia it has been found that the city-block metric provided a less beneficial data fit than in controls (Chance et al., 2011a). Therefore, alterations in the dimensions of conceptual space, consistent with disruption of lateralized cognitive processing biases, accompany abnormal anatomical structure of the cortex, including altered asymmetrical cytoarchitecture in schizophrenia.

The developmental shift from the Euclidean cognitive metric to the more separable dimensions of the city-block metric proposed by Gardenfors (2000) may be relevant in the neurodevelopmental context of schizophrenia. Although there is a clear genetic component in the etiology of schizophrenia, onset of illness is not identified until adolescence or early adulthood. It has been proposed that, structurally, this may be linked to the time course of myelination (Crow et al., 2007; Chance et al., 2008). Functionally, it may be linked to the shift in cognitive metric and as dimensionalization matures the anomalies associated with psychosis are exposed, leading to the recognition of "onset" and diagnosis.

Schizophrenia patients sometimes have difficulty in recognizing their own face (Kircher et al., 2003) and minicolumns have also been shown to be altered in the fusiform gyrus in patients (Di Rosa et al., 2009). In another neuropsychiatric condition, people with autism have a selective deficit in perceiving facial expressions categorically (Teunisse and de Gelder, 2001) which affects activation of the fusiform gyrus (Pierce et al., 2004). One of the few neuropathological features of the disorder is altered minicolumn organization (Casanova et al., 2006) accompanied by altered neuron density in layer III of the fusiform gyrus (Van Kooten et al., 2008). Although it is not, so far, apparent that the effect in autism is asymmetrical between the hemispheres, it is clear that these alterations present a risk of disruption to the very structures that support lateralized face processing and are consistent with atypical processing in that functional domain. Indeed, attempts to characterize the deficits in ASD at a broader level led to the "weak central coherence" hypothesis (Frith, 1989) which proposes that the core difference in ASD involves poor integration of "featural" information into a coherent whole.

In terms of language and theory of mind, autism is associated with excessively literal interpretation of word meaning and under-interpretation of social relevance at the pragmatic level. Both appear to emerge from a disruption of the ability to interpret layers of meaning and their relations to each other. Altered processing of semantic categories has been implicated in autism (Gastgeb et al., 2006; although further studies have suggested that the effects are often subtle). More broadly, in visual categorization tasks, deficits in prototype formation have been indicated (Gastgeb et al., 2012) and altered influence of categorical knowledge in autism has been interpreted as a reduction of top-down influence on perceptual discrimination (Soulières et al., 2007). In the context of altered minicolumn structure, these effects are consistent with the mechanistic model of minicolumn asymmetry influencing different levels of processing that are lateralized for some functions.

In contrast to autism, schizophrenia is associated with over-interpretation of word meaning at the semantic level and over-interpretation of relevance at the level of pragmatic competence, Altered interhemispheric connections have been found to be correlated with minicolumn asymmetry in auditory language cortex in schizophrenia suggesting a link to language-processing anomalies that occur in the disorder (Chance et al., 2008; Simper et al., 2011). Therefore, both disorders may involve a contribution from disequilibrium in the processing of local and global features related to the disorganization of minicolumnar units of processing.

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Inferring common cognitive mechanisms from brain blood-flow lateralization data: a new methodology for fTCD analysis

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Current neuroimaging techniques with high spatial resolution constrain participant motion so that many natural tasks cannot be carried out. The aim of this paper is to show how a time-locked correlation-analysis of cerebral blood flow velocity (CBFV) lateralization data, obtained with functional TransCranial Doppler (fTCD) ultrasound, can be used to infer cerebral activation patterns across tasks. In a first experiment we demonstrate that the proposed analysis method results in data that are comparable with the standard Lateralization Index (LI) for within-task comparisons of CBFV patterns, recorded during cued word generation (CWG) at two difficulty levels. In the main experiment we demonstrate that the proposed analysis method shows correlated blood-flow patterns for two different cognitive tasks that are known to draw on common brain areas, CWG, and Music Synthesis. We show that CBFV patterns for Music and CWG are correlated only for participants with prior musical training. CBFV patterns for tasks that draw on distinct brain areas, the Tower of London and CWG, are not correlated. The proposed methodology extends conventional fTCD analysis by including temporal information in the analysis of cerebral blood-flow patterns to provide a robust, non-invasive method to infer whether common brain areas are used in different cognitive tasks. It complements conventional high resolution imaging techniques.

Keywords: Tower of London, music, temporal patterns, hemodynamics, middle cerebral artery, cued word generation, language, lateralization

INTRODUCTION

Functional TransCranial Doppler (fTCD) ultrasound scanning is a well established technique for the robust measurement of cerebral lateralization during cognitive tasks (Knecht et al., 1998a,b; Deppe et al., 2004). It offers reliable measurements of the precise time course of cerebral blood flow changes, using portable equipment that is not susceptible to motion artefacts (e.g., Uomini and Meyer, 2013), but provides very limited spatial information.

Complementary to this, fMRI provides very high resolution imaging data that can be used to map brain areas (Newman et al., 2003; Jansen et al., 2006; Price, 2010; Meyer et al., 2011), network connectivity (Basser and Jones, 2002; Beer et al., 2013), and to decode representational content using techniques such as multi voxel pattern association (Norman et al., 2006) during specific tasks. While there is no question that fMRI is the benchmark experimental technique in cognitive neuroscience, it has a number of drawbacks, chiefly its sensitivity to participant motion (Seto et al., 2001), which requires participants to lie motionless while executing tasks.

Tasks that require participants to produce actions that can cause head movements inside the scanner are therefore a particular challenge for fMRI. FTCD has been shown to provide highly replicable measurements while participants perform actions that range from simple actions, such as elbow flexion/extension (Salinet et al., 2012), or speaking (Bishop et al., 2009) in laboratory environments, to highly energetic stone tool making (Uomini and Meyer, 2013) or driving a car in a driving simulator (Lust et al., 2011).

While fTCD has very poor spatial resolution, it provides robust temporal cerebral blood-flow signatures. Temporal data are not the focus of conventional fTCD analysis where peak blood-flow lateralization measures are reported. We propose an extension of current fTCD analysis methods that explicitly takes the temporal dynamics into account to compare blood-flow signatures for different cognitive tasks. We argue that tasks that draw on common brain areas should result in correlated activation patterns, while tasks that draw on different brain areas result in uncorrelated patterns. While the proposed analysis method is no alternative to fMRI, it provides complementary data that can be used in situations where conventional high resolution neuroimaging would not be possible, such as in natural environments, during active motion, or for participants who would be ineligible for scanning. Blood-flow signatures for tasks or participant groups that would not be suitable for conventional scanning can be directly compared with appropriate benchmark data to infer whether common processing networks are used.

fTCD OVERVIEW

FTCD measures blood flow velocity and volume changes in the major arteries supplying the brain (Deppe et al., 1997, 2000; Duschek and Schandry, 2003; Bishop et al., 2009) using two small head-mounted sensors, **Figure 1**. The technique has been used extensively for language lateralization studies since 1998, providing well documented and highly replicable baseline data (Knecht et al., 1998a; Stroobant and Vingerhoets, 2001; Bishop et al., 2009; Illingworth and Bishop, 2009; Groen et al., 2012).

PARADIGM

Cerebral lateralization is measured by computing the change in bilateral blood flow velocity in the major arteries supplying the brain during the execution of specific cognitive tasks. The changes are measured by comparing multiple cycles of alternating target and rest periods that each last around 30 s.

Cued word generation (CWG), a task where participants are asked to silently think of as many words as possible starting with a given letter, has been used extensively in language lateralization studies (Knecht et al., 1998a; Deppe et al., 2004). This task is used as one of the cognitive tasks in all experiments reported here because it has a wealth of comparison data from fTCD and other imaging methodologies.

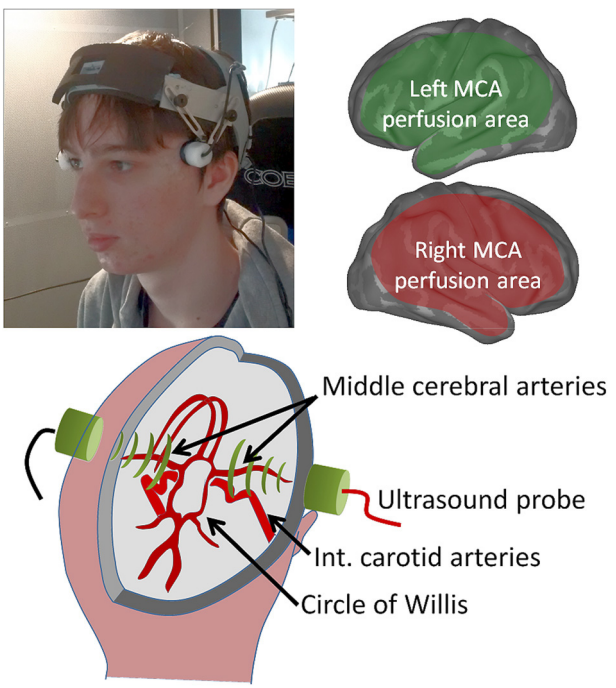


FIGURE 1 | Bilateral cerebral blood-flow is recorded using two small head-mounted probes (top left) that are relatively insensitive to participant motion. The middle cerebral arteries, insonated at a depth of ca 5 cm as they emerge from the circle of Willis (lower schematic) supply extensive regions of the cerebral cortex (top right schematic), but this excludes frontal and sagittal areas, which are supplied by the anterior cerebral artery, and occipital and inferior temporal brain areas supplied by the posterior cerebral artery.

LATERALIZATION INDEX

The fTCD lateralization index (LI) was developed to assess language lateralization in a clinical context (Knecht et al., 1998a,b). Doppler ultrasound is used to measure blood flow velocity in a pair of left and right cerebral arteries, typically the middle cerebral arteries (MCAs) supplying the brain. Relative blood-flow velocity changes compared to a baseline provide a robust estimate of the change in blood-flow volume. The LI is the difference in bilateral cerebral blood flow volume (CBFV) changes, $dV(t)$, during task execution relative to a baseline (Equation 1, adapted from Knecht et al., 1998a).

$$\Delta V(t) = dV_{left}(t) - dV_{right}(t), \tag{1}$$

where

$$dV(t) = 100(V(t) - V_b)/V_b$$

is the CBFV change relative to the mean baseline blood flow velocity (V_b), typically recorded over the 5 s preceding the target condition onset. The lateralization time course ($\Delta V(t)$) is a continuous function that changes during task execution and is specific for each individual.

The *LI*, represents the maximum absolute lateralization value, averaged over an integration interval, within the activation interval (Equation 2 adapted from Knecht et al., 1998a):

$$LI = \frac{1}{t_{int}} \int_{t_{\max}-0.5t_{int}}^{t_{\max}+0.5t_{int}} \Delta V(t)\, dt \tag{2}$$

A time period of $t_{int} = 2$ s is typically chosen as the integration interval. A positive value of the LI indicates left hemispheric processing dominance while negative values represent right hemisphere dominance. Our proposed analysis method builds on this well-established technique.

REPLICABILITY

A number of studies have shown that fTCD provides highly replicable data that match other measures of cerebral activation. Cerebral blood flow lateralization data obtained with fTCD match alternative measures, such as the relative distribution of fMRI voxel counts for cued word generation (CWG) (Deppe et al., 2000; Somers et al., 2011) and spatial attention tasks (Jansen et al., 2004, 2006). Sabri et al. (2003) showed a very high correlation between simultaneously recorded PET and fTCD lateralization data in a (n-back) working memory task. Language lateralization measured with fTCD also predicts the effect of unilateral disruption of language functions via either the intracarotid sodium amobarbital procedure (Wada test) (Knecht et al., 1998b) or repetitive Transcranial Magnetic Stimulation (rTMS) (Flöel et al., 2000).

If two cognitive tasks draw on common brain areas, which will share common haemodynamics, then one would expect highly correlated responses across a pool of participants. Bishop et al. (2009) compared the LIs obtained with the CWG task with those measured for two other language tasks that rely more on syntactic processing. They show that LIs for the CWG task are highly correlated for all three cognitive tasks, as would be expected for tasks that draw on substantially overlapping cortical networks.

It could, of course, be argued that a change from rest to any cognitive task leads to common increases in cortical activation or common attentional processes, so that correlated LIs might be expected for any pair of tasks. This is not the case. A number of studies show that visuo-spatial tasks, which draw on different brain areas than language tasks, lead to LIs that are *not* correlated with the standard CWG task: Rosch et al. (2012) tested visuo-spatial attention, Whitehouse et al. (2009), Whitehouse and Bishop (2009) used a visual memory task, while Lust et al. (2011) tested participants in a driving simulator. None of these studies found a correlation with CWG, showing that common, non-task specific processes, for example attentional modulation, are not a trivial explanation for correlated LI patterns.

Rosch et al. (2012) showed that visuospatial laterality measures were highly intercorrelated and unaffected by task difficulty, while Badcock et al. (2012) showed that for the standard CWG and an auditory naming task, performance, and reaction time measures co-varied with task difficulty while lateralization measures were not significantly different. This means that specific task demands, a difficult to control confound when two different cognitive tasks are compared, are not a sufficient explanation for the absence of correlated LI values.

CORRELATION ANALYSIS

The fundamental question we address in this paper is how individual CBFV lateralization traces can serve as the basis for inferences about common underlying brain areas that are used for *different* cognitive tasks. We argue that correlated haemodynamics provide this indication. While the LI is an appropriate measure to quantify hemispheric dominance for a given task, we argue that a comparison of peak values, the basis of the LI, is not the most appropriate measure for cross-task comparisons.

FMRI studies consistently show that, while one hemisphere is often dominant (e.g., language is typically left dominant; visuospatial processing is often right dominant), both hemispheres significantly contribute to most cognitive tasks (Bradshaw and Nettleton, 1982; Stroobant and Vingerhoets, 2001; Hickok and Poeppel, 2004; Whitehouse et al., 2009; Meyer et al., 2011; Somers et al., 2011; Groen et al., 2012; Rosch et al., 2012; Wuerger et al., 2012). A positive (left) LI for language, for example, should therefore not be interpreted as showing that language exclusively uses the left hemisphere. Instead it shows that a proportion of the underlying cognitive processes are left *dominant*.

This observation has two important implications. The first is that common overall lateralization of cerebral blood flow patterns during two tasks is not sufficient evidence for common underlying processing. It is entirely plausible that two tasks, which draw on non-overlapping brain areas, are dominant in the same hemisphere. In this case we would expect to see common overall lateralization, but not correlated CBFV patterns because each brain area has its own haemodynamics. Secondly, properly considering the LI measures as a relative dominance of cerebral activation also means that two cognitive processes can result in opposite lateralization indices for the same participants, *even if* they share significant processing. Music (right dominant) and language (left) are two well documented examples (reviews: EEG and fMRI data: Koelsch, 2012; PET data: Evers et al., 1999; Brown et al., 2006). Here both tasks draw on extensive, shared, bilateral networks but language—on average—activates more left lateralized brain areas while music draws on slightly right dominant networks. Experiment two will demonstrate this.

The analysis proposed here is based on the measured *degree* of lateralization *in a population of subjects* and follows existing cross-methodology (fMRI or PET correlated with fTCD: Deppe et al., 2000; Sabri et al., 2003) and cross-task (language vs. language/visuo-spatial/memory: Bishop et al., 2009; Whitehouse and Bishop, 2009; Whitehouse et al., 2009; Rosch et al., 2012) comparisons of cerebral lateralization.

An important methodological difference to the conventional LI analysis derives from our argument that choosing a single maximum value (the LI) as the measure of lateralization is potentially misleading because important temporal information is lost.

The time course and peak lateralization of individual fTCD recordings varies significantly between individuals, but both are highly replicable within each individual. This means that these haemodynamic variations are caused by idiosyncratic differences in the activation of brain areas rather than "noise." This is consistent with data reported in fMRI: despite the consistency of the spatially localized response patterns across subjects there is a marked, idiosyncratic variation in the timing and shape of BOLD responses across subjects (Schacter et al., 1997; Aguirre et al., 1998; Buckner et al., 2000). The source of this variability is presently unclear, but may be caused by differences in blood vessel density across regions (Lee et al., 1995), or by systematic processing delays in the underlying neuronal networks (Rosen et al., 1998).

If two tasks share common dominant brain areas, then we expect not only correlated peak lateralization values across participants, which provide the basis of the LI calculation, but we also expect lateralization *changes* to occur simultaneously for both tasks within the same participant. We therefore argue that for a principled analysis, an additional constraint should be imposed: to meaningfully compare time variant lateralization data, LI values should be correlated only within relatively narrow, synchronous analysis windows for the two tasks under consideration. We propose a moving average window of 5 s duration, which is in line with the temporal window in which BOLD responses in fMRI can be resolved (Glover, 1999; Jäncke et al., 1999).

The analysis method we propose therefore draws on the conventional LI calculation, but instead of estimating lateralization from single peak values, lateralization signatures from two tasks are compared by computing a running cross-correlation of the cerebral blood flow differences measured in successive 5 s analysis windows for a population of participants.

GENERAL MATERIALS AND METHODS

All experiments reported in this paper follow a similar experimental design and use the same recording equipment, methodology, and data analysis. This section details the aspects of experimental design and analysis that are common to all three experiments.

SUBJECTS

Participants were recruited by opportunity sampling. The majority were undergraduate students at the University of Liverpool, who were given course credits for their participation. All were healthy and without a history of neurological disorder. All had normal or corrected to normal vision and reported no hearing problems.

ETHICS STATEMENT

The experiments were approved by the University of Liverpool ethics committee (reference PSYC-1011-025—Georg Meyer—Action planning and cerebral blood flow lateralization). Written informed consent was acquired from all participants. The participant shown in **Figure 1** gave written informed consent to the publication of his image.

APPARATUS AND MATERIALS

A schematic diagram of the fTCD setup and a picture of the fTCD probes in use during an experiment are shown in **Figure 1**. Blood-flow changes are simultaneously measured in both MCAs at a depth of approximately 50 mm with a commercially available dual transcranial Doppler ultrasonography device (Multi-Dop T, DWL, Sipplingen, Germany). The two 2-MHz transducer probes were mounted on an Integra UltraLite headband (001270BIF, Integra LifeScience Corp, USA) and placed at the trans-temporal windows. The spectral envelope curves of the Doppler signals were recorded with a sample rate of 25 Hz.

EXPERIMENTAL CONDITIONS

We compare relative MCA CBFV changes during two cognitive tasks in all experiments. In both experimental conditions, target intervals were alternated with control intervals. Following standard fTCD paradigms (Deppe et al., 1997; Knecht et al., 1998a, 2000) the target intervals were 25–35 s (average =30 s) in duration while the control conditions were 15–25 s (average = 20 s) long. Twenty target/control epochs were presented in each experimental block. Stimulus presentation was controlled by a personal computer running the ShowPics software (v. 3.1.0) which was interfaced using parallel port TTL signals to the analog input of the fTCD system to mark the start of each epoch.

The CWG task, used in all experiments reported here, is a standard language lateralization assessment task used in clinical settings (Knecht et al., 2000). Subjects were asked to silently generate words starting with a letter heard at the onset of the target interval. The same letter sequence was presented to all participants in experiment 2: *[H, L, O, N, C, P, Q, T, U, Z, K, J, D, U, R, S, B, A, W, I]*. For the control interval subjects were asked to rest silently. A beep and a spoken letter marked the onset of the target interval while an isolated beep indicated the start of the control interval. In contrast to many CWG paradigms, our participants were not required to report words verbally, so that CWG and rest blocks alternated in direct succession.

The same number (20) and timing of target and control intervals was used in all experiments. Each cognitive task, e.g., 20 trials of CWG, was carried out as a separate block lasting approximately 15 min. The order of blocks within each experiment was randomized to control for order effects.

DATA ANALYSIS

The recordings were integrated over the corresponding cardiac cycles, segmented into epochs and then averaged off-line using the AVERAGE V1.85 software (Deppe et al., 1997). Trials with physiologically implausible CBFV changes relative to baseline of ±30% were excluded from the analysis. Subjects with less than 80% "good" epochs in any one of the conditions were excluded from the data analysis to ensure data integrity. The raw blood flow data are integrated over cardiac cycles, so that the CBFV signal is characterized by successive constant segments with sudden (high frequency) transitions at the time when heartbeats are detected. The average responses were filtered off-line using a second order zero-phase lag Butterworth low-pass filter to remove these high frequency components. A cut-off frequency of 1 Hz, the Nyquist limit for sampling at relatively high heart rates of 120 bpm (2 Hz), was used to ensure that haemodynamic responses were retained. All CBFV changes are computed relative to a baseline that was the average of the 5 s period immediately preceding the target epoch onset. Group statistics were computed using purpose-designed MATLAB (The Mathworks, Natick, MA) scripts.

CBFV lateralization differences (LIs) are computed not at the maximum LI, but for each sample in the measurement time series, for the average CBFV difference in a $t_{int} = 5$ s interval. The LI value is computed separately for each participant, p, and for each of the two conditions, c, to be compared.

$$LI(p, c, t) = \frac{1}{t_{int}} \int_{t}^{t+t_{int}} \Delta V(t)\, dt \tag{3}$$

Two series, one for each of two cognitive tasks (c_1 and c_2) that were executed by the same participants ($P = [p_1..p_N]$) can then be correlated to obtain a running similarity measure

$$R_{c1,c2}(t) = r\left(LI_{P,c1}(t), LI_{P,c2}(t)\right)$$

where *r(x,y)* is the Pearson product-moment correlation coefficient.

VALIDATION EXPERIMENTS

The aim of this paper is to show that the proposed methodology enables a principled comparison of CBFV change data for a population of participants within and across tasks.

We make the case that the time course, and with it the peak value and latency, of the haemodynamic response varies systematically with the specific brain areas each individual uses to perform cognitive tasks, and their blood flow patterns. These idiosyncratic responses, however, are highly replicable. Tasks that draw on the same or substantially overlapping brain areas will therefore result in similar cerebral blood-flow signatures. We argue that a time-locked, moving cross-correlation of CBFV differences across a participant pool is an appropriate analysis method.

In experiment 1 we show that the proposed analysis provides results that are comparable to those obtained with the conventional LI calculation. CBFV signatures for the CWG task stay highly correlated throughout the task interval when the task difficulty is manipulated.

In a second experiment we correlate CWG lateralization signatures with those for a music synthesis task and an abstract

problem solving task, the Tower of London (ToL) problem. We expect the CBFV signatures for the language and music tasks, which have previously been shown to draw on overlapping brain areas, to be highly correlated. Conversely, we expect the CBFV signatures for the CWG and the ToL tasks to be uncorrelated because both tasks have previously been shown to draw on different brain areas.

EXPERIMENT 1: THE EFFECT OF TASK DIFFICULTY ON LATERALIZATION MEASURES

The Lateralization Index (LI) for the CWG task measured with fTCD has been shown to be highly replicable (Knecht et al., 1998a,b; Deppe et al., 2000; Flöel et al., 2001; Jansen et al., 2004). Rosch et al. (2012) argue that LIs obtained for lateralized visual attention are not influenced by task difficulty, while Schuepbach et al. (2007) provide evidence that early modulation of cerebral blood flow is correlated with performance and thereby task difficulty. The two claims are not contradictory because the LI measures the peak cerebral blood flow lateralization over an extended interval while Schuepbach et al. (2012) performed a much more detailed analysis of blood flow patterns during early stages of the responses where mean lateralization values typically lie below the peak values used for the LI calculation.

The cued word paradigm requires participants to recall words starting with a letter chosen from a random letter sequence. Some letters, for example C, R, S, and T, are much more common at the beginning of words than others (V, X, Y, Z) so that the choice of letters can be used to manipulate CWG task difficulty.

To create two lists of CWG starting letters (easy and hard), a group of 13 participants (mean age = 20.7 years, range = 20–26) was asked to loudly generate as many words starting with each cue letter in the alphabet as possible. The average number of words recalled for each 30 s period was counted and used to split the letters into "easy" letters (words starting with [P, B, L, H, W, E, F, C, T, O, V, R, M, G] average = 6.24 words/30 s, $SD = 0.41$ words generated) and "hard" letters (words starting with [Z, X, K, I, Q, Y, J, A, S, U, D, N], avg = 4.58 words/30 s, $SD = 1.03$ words generated). A paired t-test confirmed that these two sets led to significant performance differences [$t_{(12)} = 8.971, p < 0.001$].

In the fTCD experiment, CBFV changes in the MCAs were measured in 20 participants (mean age = 21.3 years, range = 18–38) using the standard procedure outline above. In each of the conditions participants were asked to silently generate as many words as possible starting with the cue letter.

The average cerebral blood flow data for our group of 20 participants, **Figure 2**, shows a typical pattern for the CWG task. Activity in both MCAs rapidly increases over the initial 5 s of the CWG task condition. After the initial increase, the CBFV patterns in the two hemispheres diverge. The graphs show the mean CBFV change (**Figure 2**, top) and the difference between the left (L) and right (R) MCA CBFV. The standard error across all participants is shown as the colored bands around each line. The time course and magnitude of the mean data are consistent with previously reported data for the same task.

There are a number of ways to compare lateralization data across tasks or conditions. Rosch et al. (2012) directly compared the peak LI within the same participants. A paired t-test of the LI data plotted in **Figure 3** shows no significant difference between the easy and hard condition (mean LI value easy = 2.28%, $SD =$ 2.60%; mean LI value hard = 2.85%, $SD = 2.15\%$; $t = -0.84$, $df = 38$, $p = 0.4$), consistent with data reported by Rosch et al. (2012) for a visual attention task. The LI values (**Figure 3**, left panel) are highly correlated ($r = 0.83$, $n = 20$, $p =< 0.0001$). It is, however, worth remembering that the LI is the maximum CBFV change difference during the task execution, irrespective of where this maximum occurred. The graph on the right of **Figure 3** shows not the LI values, but the time (in seconds after task onset) where the peak value occurred: the majority of LI values (14/20) come from comparable positions toward the end of the task interval as expected, but for three participants the peak lateralization occurred quite early (<6 s after task onset) in both conditions. For another three participants (A–C, marked by arrows) the LIs were taken early during task execution in the easy condition, but late in the hard condition. We contend that this is not a meaningful comparison.

Duschek et al. (2008) investigated the relationship between rapid cerebral haemodynamic modulation and attentional performance. They demonstrated that blood flow relatively early in the stimulus interval (2–3 s after onset) was correlated with performance. This was not the case for the very early and late components of the response.

Our own data (**Figure 2**) show that the mean CBFV in the right MCA is not affected by a modulation of the task difficulty while the left MCA response differs during the early part of the response. In the easy condition, the left MCA response is slightly smaller and later than the right MCA response causing a dip reflecting a slight right lateralization bias on average that is visible between 0 and 5 s. In the hard condition this dip is not visible in the LI data. A direct pairwise comparison of the data shows a significant difference between the lateralization traces recorded during easy and hard CWG tasks between 2 and 3 s after task onset [mean CBFV difference easy= −0.16%, $SD = 1.09$; hard = +0.32%, $SD = 1.1$; $t_{(38)} = 1.71$, $p = 0.048$]. This finding is consistent with Duschek et al. (2008) and in our view strengthens the case for a careful consideration of the temporal aspects of the haemodynamic response.

Figure 4 shows the result of the correlation analysis we propose for comparing CBFV changes across tasks or task difficulty. Instead of correlating the (peak) LI values, we correlate the average CBFV difference within a succession of moving 5 s windows. The correlation could be computed at an a-priori defined small number of key comparison points, such as key points in the response or could be sampled continuously. Here we show continuous 5 s windows with start times between 5 s before the task onset (−5 s) and 20 s after the task onset.

The left hand graph shows correlation values, computed for a succession of $\Delta V(t)$ values averaged over a succession of 5 s long analysis windows with the indicated start times. For the two conditions the data are uncorrelated before the task onset, but during task execution highly correlated lateralization patterns are seen, as would be expected since the underlying task, and therefore the corresponding blood flow signatures, are essentially the same.

The right hand panel in **Figure 4** shows highly correlated average lateralization patterns across the two conditions computed

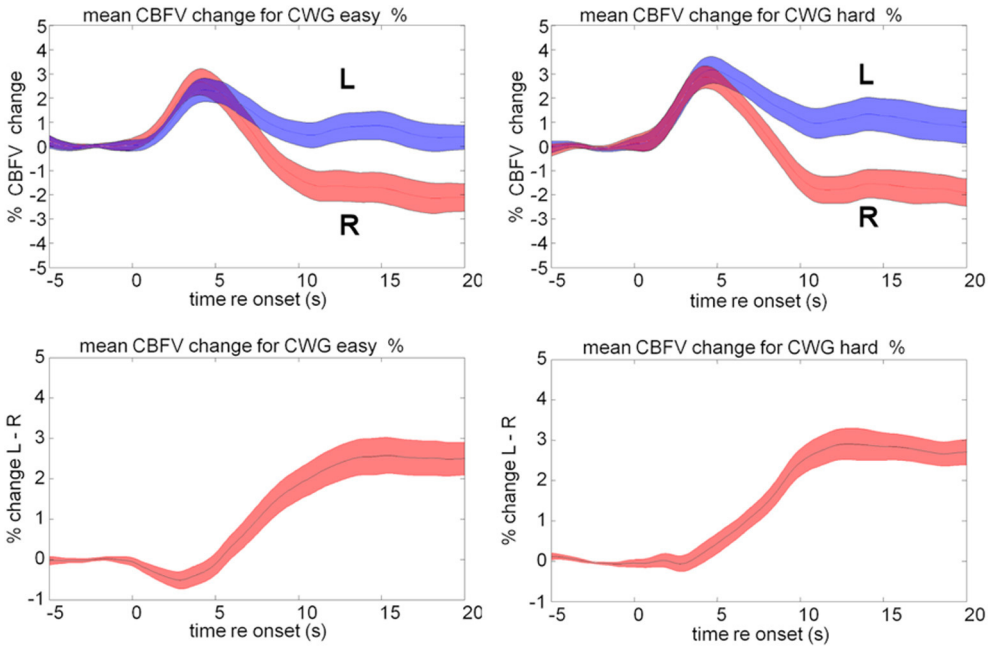


FIGURE 2 | Mean cerebral blood flow velocity (CBFV) change (%) in the left (blue) and right (red) middle cerebral arteries (top panels) during the hard and easy cued word generation tasks. The bottom panel shows the difference between left and right in CBFV changes.

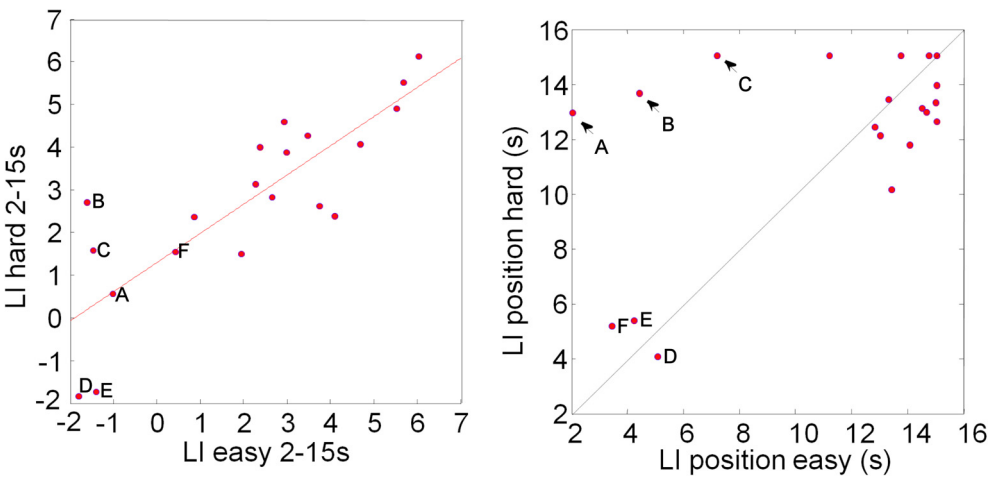


FIGURE 3 | Plot of Lateralization Indices (LI) computed for each participant in the easy and hard condition (left). The data show highly correlated ($r = 0.83$, $n = 20$, $p =< 0.0001$) LIs. The LIs are computed by averaging the CBFV difference in a window, here 2 s, around the absolute peak value in the analysis window, here 2–15 s post task onset. This means that, when LIs for two conditions or tasks are compared, the peak values do not have to coincide. The right hand graph shows the position of the windows that are the basis for the LI analysis: in the majority of cases LIs derive from similar positions between 10 and 15 s after task onset; for three individuals (A–C) peak LI values were found toward the end of the hard task conditions, but at the beginning of the "easy" conditions (arrows in right plot); for another three participants LIs were computed for relatively early responses (around 4 s) in both tasks. We argue that for a meaningful correlation analysis, matching time windows should be considered.

over the entire task interval (2–18 s post onset, $r = 0.76$, $n = 20$, $p = 0.0001$). The fact that the average CBFV over this long analysis interval shows a stable correlation between the two tasks is consistent with the continuous correlation in short analysis windows shown in the left panel. The correlation values are comparable with those obtained on the basis of the peak lateralization and show that the selection of only the peak value is not an essential feature of the analysis.

Summary

The data show highly correlated cerebral blood flow lateralization patterns for the duration of the task for two experimental

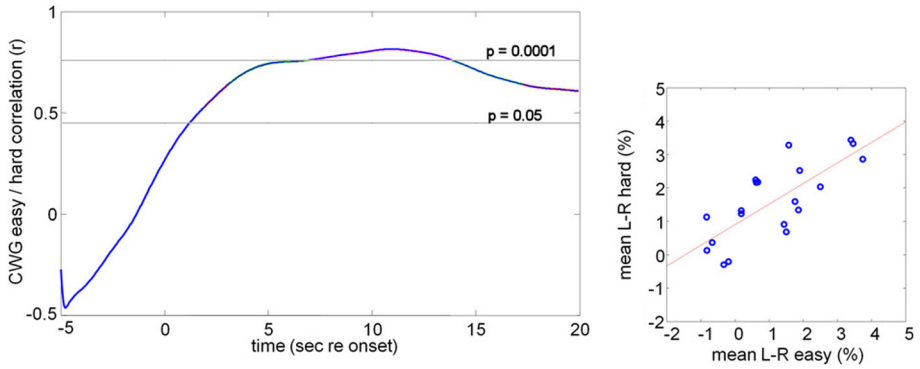


FIGURE 4 | Correlation of mean lateralization data. The right hand graph shows the mean CBFV difference within 2–15 s after task onset for all participants. The data for the easy and hard conditions are highly correlated ($r = 0.76$, $n = 20$, $p = 0.0001$). This analysis assumes constant lateralization patterns over the entire duration of the analysis window. An alternative analysis is to compute the correlation between two conditions or tasks using a moving window of limited duration, here 5 s. The correlation coefficient is plotted against the start position of the moving analysis window (left hand graph). For this comparison we see a peak correlation of $r = 0.81$ ($p < 0.0001$) at 10 s after task onset.

conditions that differed significantly in task difficulty. This correlation is seen in a conventional LI analysis, but it is also seen when correlating the CBFV differences averaged over the range between 2 and 15 s, and when a succession of short term correlations with moving start points within this time range are carried out. The correlation values in the moving window analysis are significant even for windows starting only 2 s after task onset where absolute blood-flow changes are still small. The proposed analysis, therefore, is consistent with alternative methods for within-task comparisons. Our results extend the analysis to incorporate timing information, which as Duschek et al. (2008) have shown provides relevant information.

EXPERIMENT 2: INFERRING COMMON PROCESSING NETWORKS FROM CORRELATED CEREBRAL BLOOD FLOW LATERALIZATION DATA

The aim of this paper is to show that different cognitive tasks that draw on common brain structures result in correlated cerebral blood-flow lateralization signatures. To this end we compare CBFV data for the "ToL" task and a music synthesis task with the CWG task introduced in experiment 1.

We hypothesize that language and music tasks, which have previously been shown to invoke substantially overlapping networks, will result in correlated CBFV data, while language and general abstract problem solving, exemplified by the ToL task, draw on largely distinct processing networks and should therefore result in uncorrelated CBFV signatures.

A summary of the major brain areas activated by language, music, and the ToL task is given in **Figure 5**. The music and ToL tasks are discussed in more detail in the following sections.

The Tower of London

One of the standard tasks used to assess executive/planning processes and in particular visuo-spatial processing is the ToL task (Shallice, 1982; Baker et al., 1996). Behavioral data show that visuo-spatial abilities significantly predict TOL performance and that visuo-spatial, but not verbal, memory tasks interfere with ToL planning (Cheetham et al., 2012).

Frauenfelder et al. (2004) used fTCD to measure blood flow changes during the "Stockings of Cambridge" (SoC) task (Owen et al., 1990), a computer-screen based version of the ToL task, and found differences during planning and execution relative to a control condition where subjects were required to copy previously executed moves.

Neuroimaging studies (e.g., Newman et al., 2003, 2009) have shown that the ToL problem-solving task engages a large-scale, right dominant network of cortical regions, in particular the superior parietal and dorsolateral prefrontal cortex, but also inferior frontal gyrus and the inferior parietal cortex. This activation pattern shows overlap with the circuit invoked in CWG only in the inferior frontal gyrus (BA 45 46) (Chee et al., 1999; Buckner et al., 2000). We therefore expect the two tasks to cause lateralization to opposite sides of the brain and expect the lateralization data not to be correlated across participants.

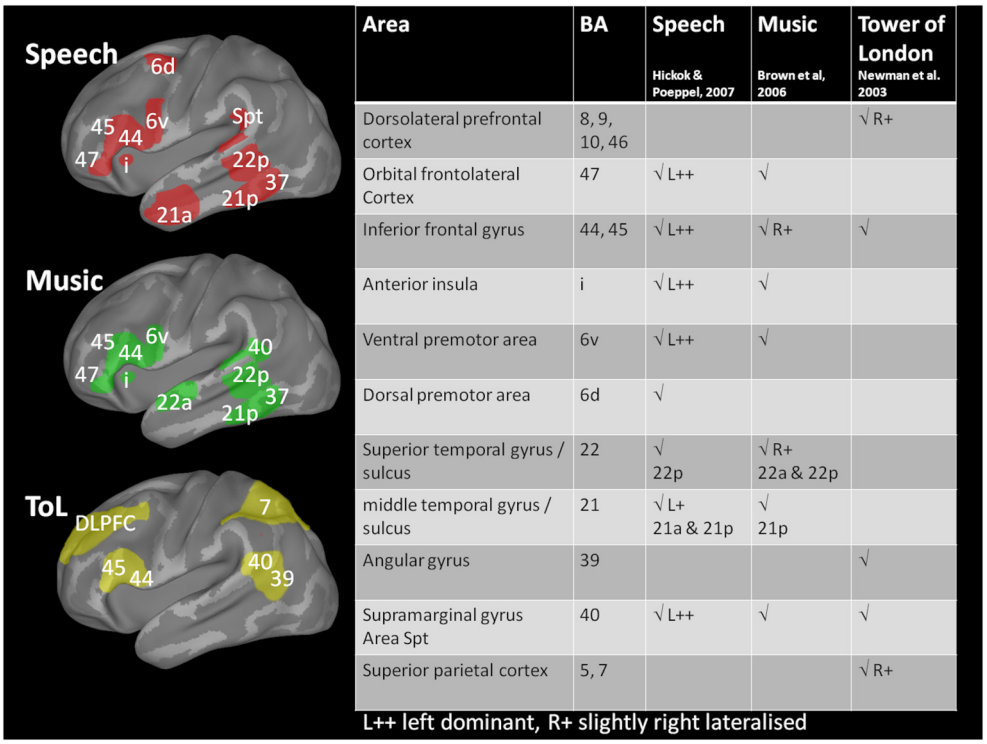
The Tower of London Task

In the target condition participants were presented with a series of boards that had three colored tokens in the start configuration and a printed depiction of the target condition. Participants were asked to plan their moves before execution. As soon as a participant solved one puzzle, the next was presented, **Figure 6** (top).

To isolate the planning from brain activity associated with moving the tokens on the board subjects were presented with a board containing a random sequence of the three token colors and were asked to move the tokens, one at a time, from their current position to the next matching square in the sequence, **Figure 6** (bottom). As before 20 pairs of target and control conditions alternated within the experiment.

Music Perception and Generation

There are several arguments linking musical processing and language that range from a phylogenetic role in the evolution of language (review: Peretz and Zatorre, 2005), the ontogenesis of infant language (e.g., Trehub, 2003), to functional neuroimaging studies that show a close correspondence of brain areas involved in music and language processing (e.g., Koelsch et al., 2002;



Area	BA	Speech Hickok & Poeppel, 2007	Music Brown et al, 2006	Tower of London Newman et al. 2003
Dorsolateral prefrontal cortex	8, 9, 10, 46			√ R+
Orbital frontolateral Cortex	47	√ L++	√	
Inferior frontal gyrus	44, 45	√ L++	√ R+	√
Anterior insula	i	√ L++	√	
Ventral premotor area	6v	√ L++	√	
Dorsal premotor area	6d	√		
Superior temporal gyrus / sulcus	22	√ 22p	√ R+ 22a & 22p	
middle temporal gyrus / sulcus	21	√ L+ 21a & 21p	√ 21p	
Angular gyrus	39			√
Supramarginal gyrus Area Spt	40	√ L++	√	√
Superior parietal cortex	5, 7			√ R+

L++ left dominant, R+ slightly right lateralised

FIGURE 5 | Schematic diagram of brain activations associated with the three tasks. Brodmann areas activated by language tasks are shown in red (from Hickok and Poeppel, 2007); very similar areas, but less left lateralized are involved in music perception and generation tasks (green, from Brown et al., 2006). Solving the Tower of London problem (yellow, from Newman et al., 2003) draws on different, frontolateral and parietal areas. The areas marked delineate Brodmann areas on an inflated brain representation (drawn with Caret, van Essen et al., 2001); primary sensory or motor areas are not shown. Activation is typically bilateral except where marked L++ for speech stimuli.

Hickok et al., 2003; Levitin and Menon, 2005; Patel, 2003; Koelsch, 2005; Brown et al., 2006; Fedorenko et al., 2009; Abrams et al., 2011).

If language and music draw on largely overlapping processing networks, then the haemodynamics observed during activation changes in similar tasks should be correlated across individual observers.

The Music Synthesis Task

The Korg Kaossilator is an electronic synthesizer controlled from a track pad, like those found on laptop computers, **Figure 7**. Users can select from 100 different sounds and modify their characteristics via the track pad: the horizontal axis is assigned to note/pitch, while the vertical axis is assigned to parameters such as cutoff, feedback, or modulation depth, allowing the creation of a very wide range of sounds.

A feature we exploit is that music is created by "loop recording": the device constantly circles through two bars (eight beats) and users can play—and record—layer after layer of music with each repeat. Players may start by recording a rhythm layer of percussive sounds, followed by the gradual addition (overdubbing) of other sounds over the existing layers. Complex music is thus created by repeating this cycle of selecting, playing, and recording sounds. Musicians have to plan their "creations" in multiple additive steps.

The synthesizer is unusual; none of our participants had used it before, but it is designed to be easy to use by novices. All participants were immediately able to produce sounds on it. The use of a small track-pad as an input device means that there are no motion artifacts.

In the target condition subjects were asked to create novel music using the Kaossilator as described above. The memory of the synthesizer was cleared after every four blocks and a regular drum beat (program 90) was preset as a start point for the task.

The CBFV signature recorded in the MCA shows the average haemodynamic modulation over a wide brain area (cf. **Figure 1**) which includes not only the action planning and musical processing, but also motor and somatosensory activity that is inherent in the manual operation of the synthesizer. To isolate action planning from rhythmic processing and hand movement related activity we asked subjects to tap out a beat, given by a metronome, in the control condition. The target and control condition alternated 20 times during each recording session as described in the general methods section.

Participants

Participants were recruited by opportunity sampling or via an experimental participation programme in the School of Psychology at the University of Liverpool and were awarded

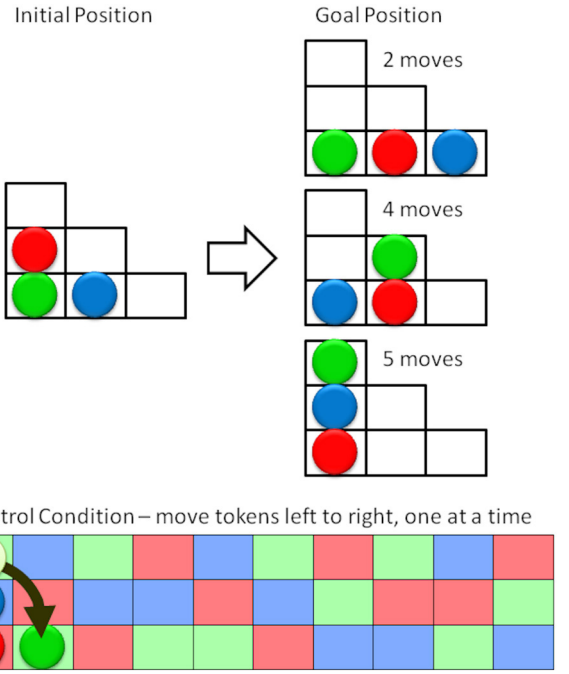


FIGURE 6 | Schematic representation of the Tower of London task (top) and the control condition (bottom). The aim is to move the three colored tokens from the initial position (left) to the goal position (right) in the minimum number of moves. Subjects were asked to first plan and then to execute their moves. In the control condition subjects were asked to move the tokens from left to right, following the color pattern. The next moves would be to move the blue token up and right, then the red token up and right, etc.



FIGURE 7 | The synthesizer used. Participants were asked to create complex sounds by layering sounds into a two bar (8 beats) phrase using a Korg Kaossilator. Sounds are selected via the wheel at the top of the device and synthesized when users touch the black pad in the lower portion of the device. The position of the finger determines the characteristics of the synthetic sounds.

course credits for their participation in the latter case. We report on data from 26 participants (mean age = 20.52, $SD = 3.5$, 15 female) for the ToL task and on 24 participants (mean age = 20.45, $SD = 2.05$, 16 female) for the music task. All participants also took part in the CWG task described previously. The difference in participant number was due to the strict exclusion criteria we used in the fTCD analysis, which meant that participants with less than 80% of accepted trials during a given task were excluded from the analysis for this task. Data from the majority of participants (21) were available for all three conditions.

For further analysis we categorized our participants as being musically experienced if they had formal musical training for more than 1 year at any point in their life (14). All participants self-reported to be right-handed, all used the right hand to move the token in the ToL task, and all exhibited left lateralized responses during the CWG task. The same subjects performed all three tasks in quasi-random order. The entire recording session took approximately 1 h.

fTCD Data Analysis

Our fTCD data are consistent with the neuroimaging data discussed above. The language task results in a typical mean activation pattern resulting from a sustained CBFV increase in the left hemisphere while an early transient right lateralized increase in blood-flow is not sustained. The ToL task causes opposite lateralization data: here blood-flow changes are larger for the right hemisphere than for the left, **Figure 8**.

Figures 9A–C show the mean CBFV changes averaged over 5 s starting at 2, 6, and 10 s after task onset for the CWG and ToL tasks. The correlation of the average CBFV values in moving 5 s windows is shown in the top left graph. The two data sets are never significantly correlated. A peak correlation value ($r = 0.24$, $df = 24$, $p = 0.25$) is seen at 11.2 s after task onset. This dataset extends existing data demonstrating that tasks that draw on different processing networks lead to CBFV patterns that are not correlated.

While the ToL and CWG tasks share few common processing areas in the brain there is a significant body of evidence that links the processing of music and language to common circuits, in particular for trained musicians (Koelsch et al., 2002; Koelsch, 2005; Steinbeis and Koelsch, 2008). The processing of music, however, is not left lateralized, but draws on bilateral cortical areas with a slight bias to the right. As in previous experiments the mean data hide a significant amount of idiosyncratic variation between participants, **Figure 10**. The range of CBFV data is clearly visible in the mean data, **Figure 11**. The running cross-task CBFV correlation (**Figure 11**) shows that the two datasets are significantly correlated over the entire period of task execution. A peak correlation value ($r = 0.654$, $df = 22$, $p = 0.0007$) is seen 5 s after task onset. The data show that the lateralization patterns in all

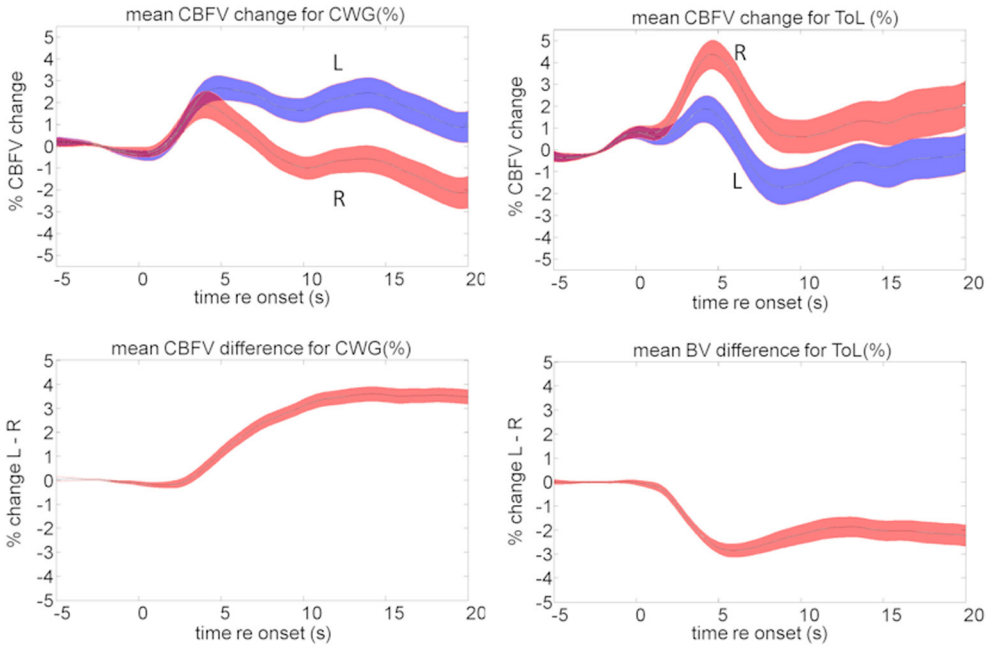


FIGURE 8 | Mean cerebral blood flow changes (top) and lateralization pattern (bottom) for the cued word generation (CWG, left) and Tower of London (ToL, right) task. The shaded area defines the standard error over all subjects. The average data shown here hide a significant amount of inter-subject variability that forms the basis of further analysis.

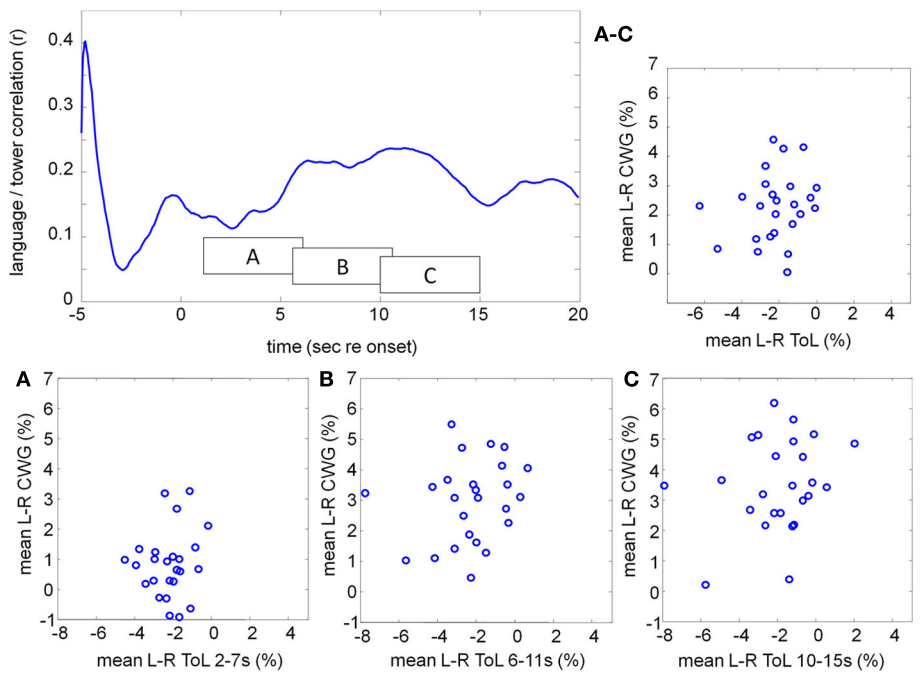


FIGURE 9 | Correlation between the mean lateralization for CWG and ToL computed across our participant pool using moving windows of 5 s duration (top left). The individual lateralization values for the two tasks are never significantly correlated. The average lateralization data in three windows, starting at 2, 6, and 10 s after task onset are shown in boxes A, B, C. The average lateralization for each subject between 2 and 15 s re task onset is shown on the top right **(**labeled **A–C)**.

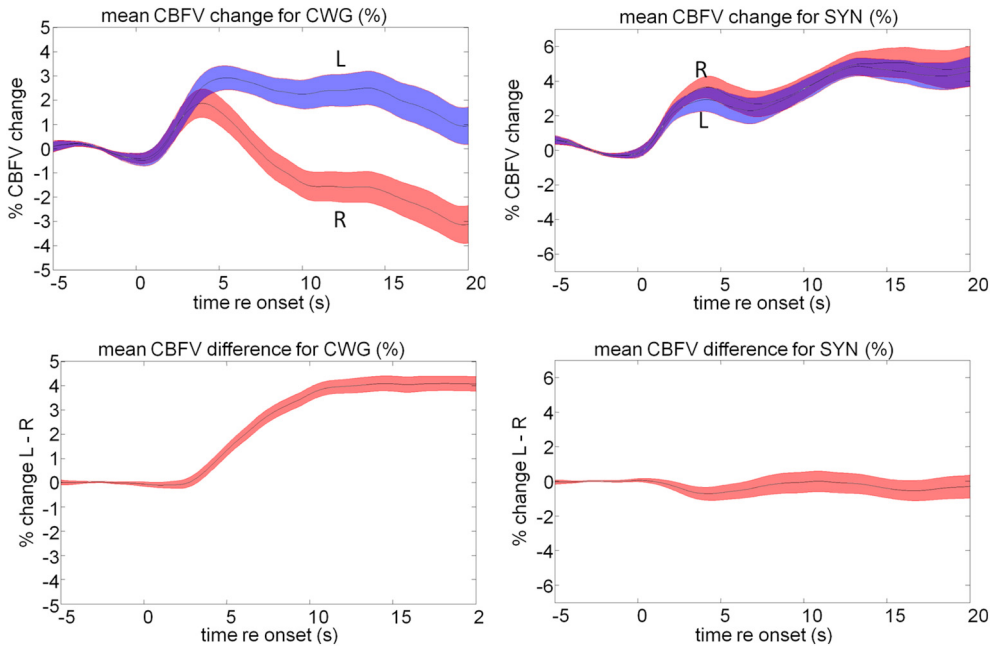


FIGURE 10 | Mean cerebral blood flow changes (top) and lateralization pattern for the cued word generation (CWG) and music synthesis (SYN) tasks. The shaded area defines the standard error over all subjects. The average data shown here hide a significant amount of inter-subject variability that forms the basis of further analysis.

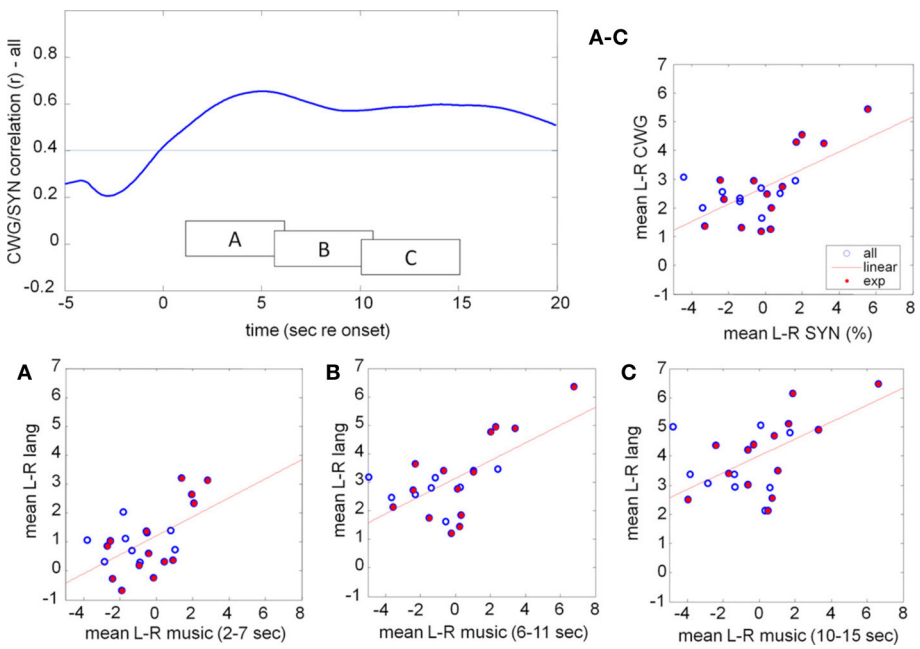


FIGURE 11 | Correlation between the mean lateralization for CWG and music computed across our participant pool using moving windows of 5 s duration (top left). The individual lateralization values for the two tasks are significantly correlated (faint line indicates the $p = 0.05$ threshold) for all analysis windows starting between 0 and 20 s after task onset. The raw data in three windows, starting at 2, 6, and 10 s after task onset are shown in boxes A, B, C. The average lateralization for each subject between 2 and 15 s re task onset is shown on the top right **(**labeled **A–C)**. CBFV for the language task predicts CBFV for music synthesis very well. Participants who received at least 1 year of musical training are marked by the filled red dots.

three analysis windows are positively correlated with a slope of approximately 0.33 in all windows.

An important observation is that, while blood-flow is strongly left-lateralized during the CWG task, the music task leads to significant sustained bilateral activity and little overall LI. The correlation analysis, on the other hand, shows highly significant correlations of CBFV for the two tasks. This means that relative LIs are maintained for individuals across the group: those participants who were most strongly left lateralized during the language task also were most left lateralized during music synthesis. Participants who were least left lateralized for language were most right lateralized for music. No participant was right lateralized for language.

The observed lateralization pattern, therefore, should not be interpreted as indicating which hemisphere is used for a particular task; instead it represents the balance of bilateral blood-flow changes. We argue that for this reason, analyses where participants are categorized as being left or right lateralized before further analysis is carried out, are not appropriate.

Evers et al. (1999), on the basis of fTCD data, suggest that musicians and non-musicians have different strategies to lateralize musical stimuli: non-musicians exhibit a delayed but marked right hemisphere lateralization during harmony perception while experienced musicians show enhanced left hemisphere lateralization in an attentive mode of listening. This difference in activation patterns between experienced and inexperienced musicians is also seen in EEG and fMRI studies (Koelsch, 2005; Lahav et al., 2007; Steinbeis and Koelsch, 2008). Bangert et al. (2006) used fMRI to demonstrate that professional pianists showed selective BOLD increases compared to the non-musicians in a distributed cortical network while listening and fingering short piano melodies. The authors argue that a distinct musicianship-specific network, encompassing dorsolateral and inferior frontal cortex as well as superior temporal gyrus, the supramarginal gyrus, and supplementary motor and premotor areas is active in trained musicians. These areas, of course, also define brain areas that are active during speech perception (Meyer et al., 2011, 2013; Beer et al., 2013) and speech production (review: Hickok and Poeppel, 2004, 2007).

If a musicianship-specific network, or specific listening strategies, that share brain areas with the language network exist, then one might expect to see correlated activity for language and music in trained musicians, but not without prior training. Of our 23 participants 14 had received formal musical training for more than 1 year at some point in their life (red filled circles, **Figure 11**) while another nine had not (open circles).

The running correlation (**Figure 12**) shows that the participants with prior musical training (experienced) show significant correlation between CWG and music synthesis with a peak correlation of $r = 0.83$ ($df = 13$, $p = 0.0001$) at around 13 s post task onset while the maximum correlation that is achieved for the musical novices (at 4.4 s, $r = 0.28$, $df = 8$, $p = 0.46$) is not significant.

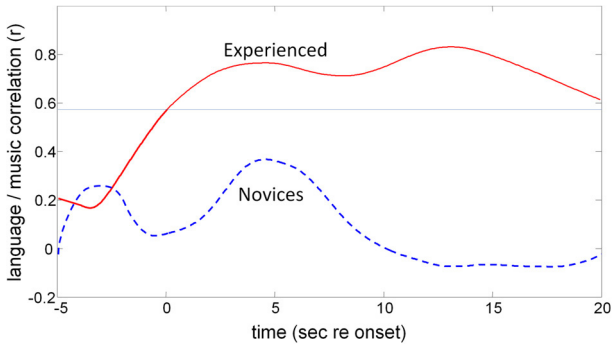


FIGURE 12 | The effect of previous musical training on CBFV correlation patterns. The two traces show the results of the moving cross-correlation between CBFV signatures for CWG and music synthesis. The top trace shows the (significant) correlation in blood-flow patterns for experienced musicians while novices (lower trace) do not show significantly correlated activity at any point of execution of the two tasks. The faint horizontal line shows the $p = 0.05$ significance threshold for the experienced participants.

Summary

The fTCD data are consistent with previously published fMRI data, which show that, on average, music perception and execution tasks draw on bilateral networks with a slight bias to the right. The processing network for music nevertheless shares many components with the network used for language processing, so that the observed correlated haemodynamic responses were expected. A number of fMRI studies showed differences in activation patterns for trained and untrained musicians, which presumably resulted from different processing strategies of the two populations for the same signals. These differences are very well represented in the fTCD data which showed that trained musicians exhibit activation patterns that are highly correlated to those seen for language while musical novices show uncorrelated patterns.

Uncorrelated lateralization patterns are also observed throughout the task execution interval when CWG and ToL data are compared. This is consistent with the hypothesis that cognitive tasks that draw on distinct processing networks lead to distinct CBFV patterns while correlated activity is an indication of common processing networks.

DISCUSSION

Functional TCD recordings, despite the idiosyncrasy of individual blood-flow signatures, are highly replicable. We report on three sets of data for the same (CWG) task that was recorded using different groups of participants and in different environments. The average responses, shown in **Figures 2**, **8**, **10** are very similar: CBFV changes are visible after around 3 s after task onset, then gradually increase over a period of 7–10 s to maximum of 2–3%, which is reached around 13 s after task onset. This makes it possible to compare the recorded data with data from the literature and to evaluate the validity of the recordings.

Individual CBFV lateralization signatures change systematically over time. We therefore argue that any analysis that compares CBFV data across conditions or tasks should take this into account. In experiment 1 we show that the correlation analysis we propose results in similarity measures that are comparable to the conventional LI analysis. We demonstrate that the conventional LI analysis, since it computes peak lateralization values for each

task under consideration, may use data from very different phases of the response and therefore may compare data from different time-points. The running correlation avoids this issue. It shows that the relative lateralization patterns for groups of participants are replicable, even at the very early stages of the CBFV response where only small lateralization changes are visible. The analysis therefore provides data that are comparable to the conventional analysis but also provide additional timing information.

For all data reported here the correlation values are obtained for each sample (25 per second) in the response. Our data, consistent with theoretical considerations (Glover, 1999; Jäncke et al., 1999), show that blood-flow changes are relatively slow. For this reason we propose analysis windows of 5 s over which lateralization data are integrated before the correlations are computed. If the time course is evaluated every 2 s, then successive windows have 60% overlap. The correlation measures we report are highly significant for tasks that draw on common brain areas (CWG/CWG; CWG and music) and clearly non-significant for tasks that draw on different areas (CWG and ToL). This means that even an aggressive Bonferroni correction of the results would not change the conclusions; more practical methods such as controlling for false discovery rate (Benjamini and Hochberg, 1995) or using a limited a-priori defined analysis points are also possibilities. The CBFV measure is computed relative to the average values during the baseline period. The inclusion of correlation analysis windows that cover this baseline period provides a useful reality-check for the analysis because in this time window only uncorrelated noise should be measured.

An important consideration when discussing lateralization of cognitive functions is to treat lateralization as a relative dominance of one hemisphere rather than as the exclusive allocation of processing resources to one side of the brain. It means that the relative degree of lateralization across tasks, rather than the location of the dominant side for individual participants, is the relevant measure as we demonstrate in experiment 2.

The conventional LI measure may contribute to the categorical interpretation of fTCD lateralization data because population studies (e.g., Knecht et al., 2000) show a bimodal distribution of LI values. This distribution, which shows few examples near zero, is an inevitable consequence of selecting the maximum values, as Badcock et al. (2012) demonstrate (their Figure 4) by comparing the distribution of mean and maximum lateralization data for the same experiment. It is easy to mistakenly interpret a bimodal distribution of LI values for language as evidence for a bimodal distribution of language lateralization. Instead we show that the mean lateralization data in synchronous time windows can be highly correlated, even if mean lateralization data and the distribution of peak lateralization data (our music/CWG data) might be taken as evidence that the lateralization for the two tasks is different.

FTCD provides data with minimal spatial resolution. In terms of neuroimaging it is clearly not a viable alternative to established techniques such as fMRI and PET. The technique, however, has a number of unique features such as its portability and robustness to participant motion that make it very well suited to complement conventional imaging techniques. The analysis we propose hinges on the assumption that, since there are significant idiosyncratic differences in the haemodynamics for each individual and each brain area, common CBFV patterns for two different tasks are an indication of the invocation of substantially shared brain areas for the processing of both tasks.

The robustness and high degree of replicability of fTCD recordings is well documented (Deppe et al., 1997; Vingerhoets and Stroobant, 2002; Whitehouse et al., 2009) for the conventional LI analysis. A number of studies also show that conventional LIs remain correlated when task difficulty for other tasks is modulated Rosch et al. (2012) and Badcock et al. (2012). Experiment 1 demonstrates that this is also the case for the CWG task and our proposed analysis method. This should not be interpreted as evidence that lateralization and task difficulty are not related, but rather that task-difficulty induced LIs in the CWG task do not affect the correlation significantly.

The main benefit of fTCD is that it can be measured relatively easily, is robust to participant motion and can be used "anywhere." Uomini and Meyer (2013), who recorded prehistoric stone tool-makers in an open air museum, demonstrate this. This means that one way in which fTCD can complement techniques such as fMRI is by demonstrating that pairs of tasks are correlated. One task could be the target task, the other could be a reference task, which is hypothesized to draw on overlapping brain areas and which can be measured using fTCD and high resolution neuroimaging techniques. CWG, for example serves as a convenient baseline task for language tasks.

Another area where fTCD can complement fMRI is for participant groups where fMRI scanning is problematic. Obvious examples include studies involving children (e.g., Whitehouse et al., 2009) or certain patient groups such as pacemaker users or cochlear implant users.

The fTCD technique and analysis are relatively easy to use and to learn, so that they are very well suited for educational projects. A significant proportion of the data described in this paper were collected as part of university projects or work experience placements for which the relative robustness and safety of the equipment and simplicity of the analysis are invaluable.

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Functional asymmetry and effective connectivity of the auditory system during speech perception is modulated by the place of articulation of the consonant – A 7T fMRI study

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To differentiate between stop-consonants, the auditory system has to detect subtle place of articulation (PoA) and voice-onset time (VOT) differences between stop-consonants. How this differential processing is represented on the cortical level remains unclear. The present functional magnetic resonance (fMRI) study takes advantage of the superior spatial resolution and high sensitivity of ultra-high-field 7T MRI. Subjects were attentively listening to consonant–vowel (CV) syllables with an alveolar or bilabial stop-consonant and either a short or long VOT. The results showed an overall bilateral activation pattern in the posterior temporal lobe during the processing of the CV syllables. This was however modulated strongest by PoA such that syllables with an alveolar stop-consonant showed stronger left lateralized activation. In addition, analysis of underlying functional and effective connectivity revealed an inhibitory effect of the left planum temporale (PT) onto the right auditory cortex (AC) during the processing of alveolar CV syllables. Furthermore, the connectivity result indicated also a directed information flow from the right to the left AC, and further to the left PT for all syllables. These results indicate that auditory speech perception relies on an interplay between the left and right ACs, with the left PT as modulator. Furthermore, the degree of functional asymmetry is determined by the acoustic properties of the CV syllables.

Keywords: functional magnetic resonance imaging, ultra high field, auditory cortex, place of articulation, VOT, dynamic causal modeling

INTRODUCTION

A vocal sound is a complex, acoustic event that is characterized by specific spectro-temporal patterns of different speech-sound elements. To perceive a vocal sound as an intelligible speech sound, and particularly to differentiate between consonants, two determining acoustic features are of importance: the "place of articulation" (PoA) and the "voice-onset time" (VOT; Liberman et al., 1958; Lisker and Abramson, 1964b; Voyer and Techentin, 2009). In contrast to vowels that are mainly tonal-sounds with a constant intonation, sounds of stop-consonants are spectrally more complex and are mainly characterized by PoA and VOT. PoA describes the spatial position and configuration of an active articulator that stops the airflow, while VOT describes the time between the release sound of the consonant and the onset of the voice for pronouncing a successive vowel. For example, the consonant–vowel (CV) syllables /da/ and /ta/ have the same PoA but differ in their VOT, as the release sound for /t/ takes longer time than for /d/. Consequently, the onset of the glottal voicing is delayed. On the other hand, /d/ and /t/ share the same configuration of the vocal tract, i.e., they have the same PoA. The PoA of the consonants /d/ and /t/ are called alveolar, with the blockage of the airflow at the alveolar ridge, /b/ and /p/ are called bilabial, since the airflow is stopped at both lips, and, finally, /g/ and /k/ are called velar, with the blockage at the velum. From an acoustic point of view, bilabial stop consonants produce a diffuse spectrum with a primary concentration of energy at 500–1500 Hz, velar stop consonants produce a high-amplitude but low-frequency spectrum with frequencies range from 1500 Hz to 4000 Hz, and, finally, alveolar stop consonants produce, through turbulences at the front teeth, frequencies above 4000 Hz (Cooper et al., 1952; Halle et al., 1957; O'Brien, 1993). Hence, phonological studies often use the stop consonants /b/, /d/, and /g/ that have a short VOT, and /p/, /t/, and /k/ that have a long VOT, and pair them with a vowel, like /a/, /o/, or /i/, to form a CV syllable. In many languages, the syllables /ba/, /da/, and /ga/ are voiced CV syllables with a short VOT, and the CV syllables /pa/, /ta/, and /ka/ are unvoiced syllables with a longer VOT (Liberman et al., 1958; Lisker and Abramson, 1964a; Rimol et al., 2006; Voyer and Techentin, 2009). As can be seen from **Figure 1**, which displays the spectrogram of two associated syllable pairs (ba, pa, and da, ta) that have the same PoA but different

VOTs, the spectral pattern differs between the four syllables. In particular, the spectro-temporal pattern over the first 30–70 ms in the frequency range between 0 and 3000 Hz is important for the differentiation of these CV syllables.

Although the differentiation between PoA and VOT is one of the most characteristic elements in the perception of speech, only a few neuroimaging studies, using either functional magnetic resonance (fMRI), electroencephalography, or magnetoencephalography, have tried to address the neuronal underpinnings of VOT and PoA differentiation [see, for example (Gage et al., 2002; Blumstein et al., 2005; Frye et al., 2007; Giraud et al., 2008; Hutchison et al., 2008; Hornickel et al., 2009)]. These studies have shown concordantly that the processing of VOT differences is predominantly performed by the left auditory cortex (AC), while the right AC may have only supporting function but does not linearly follow VOT differences (Frye et al., 2007). Gage et al. (2002) found in their MEG study a longer latency of the M100 component in the right hemisphere for /ba/ but not for /da/ and /ga/. This M100 latency effect is interpreted to reflect a different coding mechanism for syllables with different PoAs, which is also different between the hemispheres. Furthermore, PoA differentiation can already be observed on the level of the brainstem (Hornickel et al., 2009).

CV syllables are quite common in behavioral studies, similar to studies that use a dichotic presentation. Here, two different syllables are presented simultaneously to the left and right ear. Asking the participant to report the syllable they perceived most clearly or earlier, the majority of the population will report the syllable presented to the right ear, irrespective of VOT and PoA. This perceptual bias is called the "right-ear advantage" (REA; Shankweiler and Studdert-Kennedy, 1967; Hugdahl et al., 2009; Westerhausen et al., 2009b). The typical explanation for the REA is the more preponderant neural connection between the right ear and the left AC, while the ipsilateral connection is assumed to be inhibited (Kimura, 1967; Penna et al., 2007). Given that the left hemisphere is the speech dominant hemisphere in the majority of individuals, the REA is taken as a behavioral correlate of the speech lateralization (Hugdahl et al., 1997, 2009). However, taking VOT and PoA into account, it has been shown that different left-right pairings of stop-consonant CV syllables, with different VOTs and/or PoAs to the left and right ear, respectively, can modulate the strength of REA (Speaks and Niccum, 1977; Rimol et al., 2006; Sandmann et al., 2007; Voyer and Techentin, 2009). For example, syllables with long VOTs are generally reported more often, irrespective of the ear to which they have been presented (Rimol et al., 2006). Similarly, Voyer and Techentin (2009) investigated the relationship between PoA and REA, and confirmed an influence of both stimulus dominance as well as VOT on the strength of the REA with velar PoA being the most effective modulator of the REA (Voyer and Techentin, 2009).

These behavioral results could be seen as indication of a bilateral processing of speech sounds, at least on the initial perceptual level, which is also supporting recent models on speech perception (Hickok and Poeppel, 2007; Specht, 2013, 2014). However, these models also confirm the classical view of a predominant function of the left temporal lobe in processing and decoding of speech sounds, but only on a higher hierarchical level than the perception process (Specht, 2013). From animal studies as well as from neuroimaging studies in humans, it is known that the left and right ACs is processing different aspects of an acoustic signal. The left AC is assumed to have a higher spectral and thus higher temporal resolution. The right AC is assumed to integrate the acoustic signal over a longer time window and is expected to be more sensitive to the tonal aspects of a signal (Poeppel, 2003; Boemio et al., 2005). This view has been recently confirmed by electrophysiological results which showed that incoming speech signals are asymmetrically transformed into intrinsic oscillations within the AC. Within the left AC, a higher activity in the gamma frequency band (25–35 Hz) has been observed, while the right AC demonstrated more activity in the theta frequency band (4–8 Hz; Giraud and Poeppel, 2012).

Based on the afore described behavioral and neuroimaging studies, one could hypothesize that CV syllables with different VOTs and PoAs are differently processed by the left and right ACs, due to their different acoustic characteristics. More specific, the higher acoustic complexity of syllables with long VOT are expected to be stronger left lateralized than syllables with a short VOT, since the left AC is expected to have a higher temporal and spectral resolution, while the right AC might be superior in processing the more dominant tonal aspects of a CV syllable with a short VOT. Similarly, differential functional asymmetry has also been reported for PoA (see, e.g., Gage et al., 2002). Based on this, a stronger contribution of the right hemisphere was expected for bilabial than for alveolar syllables. Using a within-speech design, the aim of the present study was to investigate the functional–structural relationship as well as the functional and effective connectivity within the left and right primary and secondary ACs during the perception of CV syllables with different PoAs and VOTs.

To detect these subtle processing differences, this functional magnetic resonance imaging study requires a high sensitivity to subtle differences in the fMRI signal, as well as a reasonable high spatial as well as high temporal resolution, which can be achieved only on an ultra-high-field 7 T MRI.

MATERIALS AND METHODS

PARTICIPANTS

Ten healthy, right-handed participants (7/3 male/female, mean age 27, age range 21–39) were investigated in this study. All participants gave written informed consent in accordance with the Declaration of Helsinki and Institutional guidelines. The study was conducted in accordance with the 7 T-MR-protocols approved by the ethics committee of the University of Magdeburg. The participants were recruited from the student population at the University of Magdeburg and the employees at the University hospital Magdeburg, and they got a reimbursement of 30 €. All participants were informed about the rational of the study and they were assured that they could interrupt their participation at any time for any reason. Prior to the scanning, participant got a subject code, containing only two letters and two digits, not related to participant's name or age. In addition to sound-damping headphones, participants wore earplugs in the scanner.

STIMULI

In total, eight CV syllables were selected for this study, whereof four syllables started with a bilabial consonant and four with an alveolar

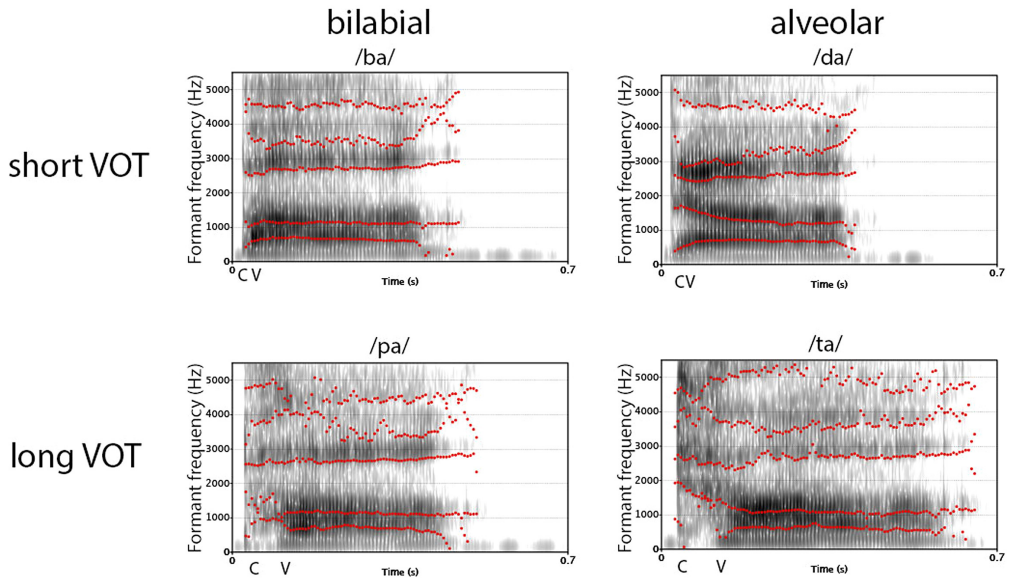


FIGURE 1 | Comparison of sound spectrogram for the four used CV syllables /ba/, /pa/, /da/. The contours of the first five formants are displayed, as revealed by the phonetic analysis software Praat (http://www.fon.hum.uva.nl/praat/). The labels "C" and "V" indicate the approximate onset of the consonant and vowel/voice.

consonant. To maximize the contrast between different PoAs, only alveolar and bilabial syllables were used, since they differ the most with respect to their initial frequency distributions (Cooper et al., 1952; Halle et al., 1957; O'Brien, 1993). The used CV syllables were /ba/, /bo/, /da/, /do/, /pa/, /po/, /ta/, and /to/, recorded from four male and four female, non-professional speakers with German as their native language. During the recording of the syllables, speakers read each syllable four times in a randomized order to avoid order effects in the pronunciation. Speakers were standing in front of two AKG 414-B condenser microphones[1], placed in an echo-reduced chamber. The recordings were made and afterwards edited with Adobe Audition 2.0[2]. Editing of the syllables contained aligning the onsets of the syllables to approximately 20 ms post-onset of the sound file as well as cutting the sound files to a total duration of 700 ms and converting them into a single channel. Using in-house software, written in MATLAB 2011b[3], the loudness of the sound files was peak normalized to the same level across speakers and syllables.

DATA ACQUISITION

All MR data were acquired on a 7T Siemens MR system, equipped with an eight-channel head coil (Rapid Biomedical GmbH, Rimpar). Prior to the acquisition of the functional data, a B1 map was obtained, followed by a high-order shim, a T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TE/TR/TI/FA: 5.24 ms/2000 ms/1050 ms/5) and a gradient-echo proton density image (TE/TR/FA: 5.24 ms/1430 ms/5) was acquired. Both datasets were acquired with an isotropic voxel size of 1.0 mm, a matrix size of 256 × 256, and 176 slices. In preparation of the functional images, a separate scan was acquired for estimating the point-spread function needed for the correction of echo-planar imaging (EPI) distortions, typically occurring at ultra-high-field MR systems (Chung et al., 2011). The acquisition of the functional data was separated into five consecutive runs with 220 volumes each. Each volume had 37 interleaved acquired axial slices, an isotropic voxel size of 1.4 mm, a matrix size of 160 × 160, and the EPI sequence had the following parameter: TR = 2000 ms, TE = 23 ms, and FA = 80. To get a suitable temporal resolution for the subsequent dynamic causal modeling analysis, there were no silent gaps between consecutive volumes. The volumes were oriented to cover the AC and the middle and posterior part of the temporal lobe, extending into the inferior part of the parietal lobe, most of the inferior frontal areas, and most of the occipital lobe. An online motion correction was applied during the data acquisition, using the retrospective motion correction, as implemented on MR systems.

Stimulus presentations, data logging, and synchronization with a trigger signal from the MR scanner were all controlled by Presentation software (Version 15.3[4]). Auditory stimuli were presented through MR-compatible stereo headphones (MR confon[5]). A block design was used as experimental design. Within each block, all CV syllables started with the same consonant, but vowels and voices were randomly selected out of the stimulus pool. Each run contained 3 blocks for each PoA and VOT, with 10 trials per block, and the order of the blocks was randomized for each run. Each block of 10 trials lasted 20 s, where the presentation of the syllable lasted for 700 ms, followed by a brief silent period that was

[1]www.akg.com
[2]www.adobe.com
[3]www.mathworks.com
[4]http://www.neurobs.com
[5]http://www.mr-confon.de

randomly assigned to each trial, but restricted in the way that the presentation of these 10 trials together last 20 s. There were an equal number of OFF-blocks, lasting for 16 s, without any presentations, interspersed. During the stimulus presentation phase, participants were asked to listen attentively to the presented syllables. To keep the attention of participants focused onto the syllable presentation but without requesting an active processing of the stimulus content, a few target trials were interspersed where participants were instructed to press a button whenever the sound was presented to the left or right ear only (Specht et al., 2009; Osnes et al., 2011). Therefore, one trial of each block was randomly selected as target trial, where the sound was presented only to one ear. However, these were only 10% of all presented trials, while the other trials were presented bilaterally, where no response was required. In the subsequent analyses, only these non-target trials were considered, where subject attentively listened to the trials but without a motor response. To respond, participants had a response button in their left and right hands. There was no other visual stimulation during the scanning, but subjects were instructed to keep their eyes open.

DATA ANALYSIS

The fMRI data were processed and statistically analyzed, using SPM8 (SPM = Statistical Parametric Mapping[6]). Prior to the statistical analysis, the data were pre-processed, including the following processing steps: first, a slice-time correction was applied. Although the data were already corrected for head movements and distortions during scanning, possible remaining head movements and head-movement-related image distortions (unwarp) were estimated and corrected using the SPM8 standard procedures but without using an additional phase map. Corrections were made within and across the five runs, using the first image of the first run as reference. Since the images were corrected for geometrical distortions, the fMRI data were co-registered with the anatomical T1 dataset. The latter one was used as source for estimating the stereotactic normalization to a standard reference brain, as defined by a template created by the Montreal Neurological Institute (MNI). This normalization was achieved through, first, a correction of the inhomogeneous distribution of image intensities and thereafter segmentation, using the unified segmentation approach, as implemented in SPM8 (Ashburner and Friston, 2005). Finally, the normalized fMRI data were resampling to a cubic voxel size of 1.5 mm, and a smoothing with a 4 mm Gaussian kernel was applied.

For the statistical analysis, a design matrix was specified that treated the five runs as one single run, by including four additional regressors in the design matrix that accounted for possible baseline shifts between the runs. In preparation of the dynamic causal modeling (DCM) analysis, the data were not modeled as a 2 × 2 design, but rather as an event-related design with two conditions, where the first condition modeled all effects of interest as a parametric design, and the second condition modeled only the target trials, which were not further analyzed, since this task was only included to keep the attention of the participants more constant throughout the study. The first condition was based on the onset of each stimulus, irrespective of PoA or VOT. Without the target trials, these were 540 trials. This main condition is further called the "phonetic input" and represents the general perception of syllables. The additional effects of PoA, VOT, as well as their interaction were added to this first condition as modulating parameters, pooling across voices and vowels. This has the advantage for the subsequent DCM analysis that the system has only one phonetic input, which is the general perception of the syllables, and the PoA and VOT effects can be used as parameter that may modulate connections strength between nodes within the modeled network. The second condition was specified for the target trials, without analyzing them further. This condition was mainly aimed to capture the motor responses, since a response was only required to these target trials. The silent rest periods between stimulations were not explicitly modeled in the design matrix. All onset vectors were convolved with a hemodynamic response function (hrf), as implemented in SPM. During the model estimation, the data were filtered with a high-pass filter with a cut-off of 256 s. Contrasts were estimated for the phonetic input condition as well as for the linear parameter PoA, VOT, and PoA × VOT interaction. Since the silent periods between stimulations were not included in the design matrix as an explicit condition, the contrast for the phonetic input represents the BOLD signal against the implicitly modeled rest condition, while the contrasts for the linear parameter reflect additional activations, on top of the phonetic input. The resulting contrast images were subjected to a second-level group statistics. One sample *t*-tests were performed for the different contrasts. The main effect for the phonetic stimulation was explored with an uncorrected threshold of $p < 0.001$ and a corrected extend threshold of $p(\text{FWE}) < 0.05$ per cluster. Localizations of the activations were explored using anatomical templates, included in the MriCron software[7], as well as using cytoarchitectonic probability maps as implemented in the SPM Anatomy toolbox (Eickhoff et al., 2005).

DYNAMIC CAUSAL MODELING

Based on the group results gained from the above analyses, five regions of interest were selected. These were the medial and lateral aspects of the AC, bilaterally and, for the left hemisphere, an area covering the planum temporale (PT). Individual time courses were extracted from each region for the most significant voxel from the single-subject analysis that was within a sphere of 8 mm around the peak voxel from the group analysis.

The individual time courses from these five regions were entered into a DCM (version DCM10) analysis. DCM is a generative, statistical approach, applying a neurodynamical model that describes the neuronal activity as non-linear, but deterministic system [see (Friston et al., 2003; Friston, 2009; Penny et al., 2010; Stephan and Roebroeck, 2012) for more details]:

$$\dot{z} = \left(A + \sum_j u_j B^j \right) z + Cu \tag{1}$$

[6]www.fil.ion.ucl.ac.uk/spm

[7]http://www.mccauslandcenter.sc.edu/mricro/mricron/

In this equation, z denotes the time course of the neuronal activity and its temporal derivative, respectively, u is the experimental input, entering the system at a specified node, while the matrices A, B, and C are defining the model. Thus, three matrices have to be defined: First, the A-matrix represents the functional connection pattern between the nodes, second, the B-matrix parameterized the context-dependent changes in connectivity (effective connectivity), and, finally, the C-matrix defines where the input signal is entering the network. By varying the B-matrix, different DCMs could be specified, forming a model space of different possible solutions, where the most probable solution could be selected by a Bayesian model selection (BMS) approach (Stephan et al., 2009).

Dynamic causal modeling rests on estimating the model evidence that is how good the model explains the data. To find the best model, several models have to be estimated and their model evidences have to be compared (Friston, 2009; Friston et al., 2013). In total, 16 models were specified and a BMS approach (Stephan et al., 2009) was applied for identifying the model with the highest evidence and posterior probability. Common to all 16 models was that the medial and lateral AC of the left and right hemispheres received the phonetic input. Furthermore, a general connection pattern was defined that assumed that an area of the AC is only connected to its neighboring area, to PT, and to its homolog on the other hemisphere, but not to its non-homolog area. For example, the left medial AC was connected to its neighboring left lateral AC, to the planum temporal, and to right medial AC, but not to the right lateral AC. This assumption was confirmed by a pre-analysis on the A-matrix, where fully connected DCM models, i.e., each node was connected to every other node, were compared to DCM models with this reduced connectivity, using a selection approach, based on model families (Penny et al., 2010). Subsequently, the most probable input nodes for these models (C-matrix) were determined in the same way.

The final set of 16 DCM models differed with respect to the modulating influence of PoA on the 16 connections, defined by the A-matrix. Thereby, the B-matrix differed between the 16 models by putting an additional, PoA-dependent weight on the respective connection, while the A- and C-matrices were identical for all models. In general, the strength of a connection is a measure of how activity in one area influences the activity in another area. BMS selection was applied to determine the model with the highest evidence and posterior probability, followed by Bayesian model averaging (BMA). The DCM analysis was restricted to PoA, since the analysis of the activation data revealed significant effects only for PoA (see Section "Results"). However, in an explorative manner, effects of VOT were explored in the same way.

FUNCTIONAL ASYMMETRY

To examine a possible functional asymmetry, a region of interest (ROI) analysis was conducted based on anatomical probability maps of the AC rather then using manually defined ROIs (Peelle, 2012). To avoid an overlap across ROIs, only the lateral area TE1.2 and the more medial area TE1.1 were considered (Morosan et al., 2001). A mask was created, representing a 50% probability of being either TE1.1 or TE1.2. Individual BOLD signal changes were extracted from these areas and data were subjected to a $2 \times 2 \times 2 \times 2$ factorial, repeated-measure ANOVA, with the factor Hemisphere, ROI, PoA, and VOT, and a Greenhouse–Geisser sphericity correction was applied.

For display purposes, data were also extracted for the left PT, based on an anatomical mask.

RESULTS

The phonetic stimulation revealed distinct activations in the left and right ACs, separating into more medial and more lateral aspects of the primary AC and adjacent, secondary areas. Using cytoarchitectonic probability maps (Eickhoff et al., 2005), these areas were identified as TE 1.0, TE 1.1, TE 1.2, and TE 3.0. In addition, there was activation within the left posterior superior temporal gyrus, extending into PT (see **Table 1** and **Figure 2**).

PoA, VOT, and their interaction were analyzed as parametric modulators, displaying those areas where additional activation

Table 1 | List of all significant activations for the phonetic perception (across all syllables) and the specific activations for alveolar syllables.

Localization		MNI coordinates			Peak			cluster	
Structure	**Cytoarchitectonic**	***x***	***y***	***z***	**p**	***Z*-values**	***T*-values**	**p(FWE-corr)**	**size (#voxel)**
Phonetic perception									
Heschl's gyrus (right)	TE 1.0, TE 1.2, TE 3.0	49.5	−13	1	< 0.001	4.49	9.20	< 0.001	1077
Heschl's gyrus (left)	TE 1.0, TE 1.2, TE 3.0	−64.5	−11.5	2.5	< 0.001	4.47	9.08	< 0.001	555
Planum temporal (left)	IPC, TE 3.0	−60	−34	14.5	< 0.001	4.30	8.28	< 0.001	228
Alveolar CV syllables									
Heschl's gyrus, superior temporal gyrus (left)	TE 1.2, TE 3.0, STG	−61.5	−8.5	−2	< 0.001	4.74	10.63	< 0.001	432
Heschl's gyrus (right)	TE 1.0 TE 1.1, IPC/PT	60	−23.5	8.5	< 0.001	4.11	7.43	< 0.001	157
Planum temporal (left)	TE 3, IPC	−64.5	−28	14.5	< 0.001	3.97	6.89	< 0.001	124

A voxel-wise threshold of $p < 0.001$ and a cluster threshold $p(FWE) < 0.05$ was applied. Activations are described in terms of cluster size [number of voxel (1.5 × 1.5 × 1.5 mm)], peak height, and the respective p-values. Furthermore, localizations of effects are described with MNI coordinates, anatomical and cytoarchitectonic structure.

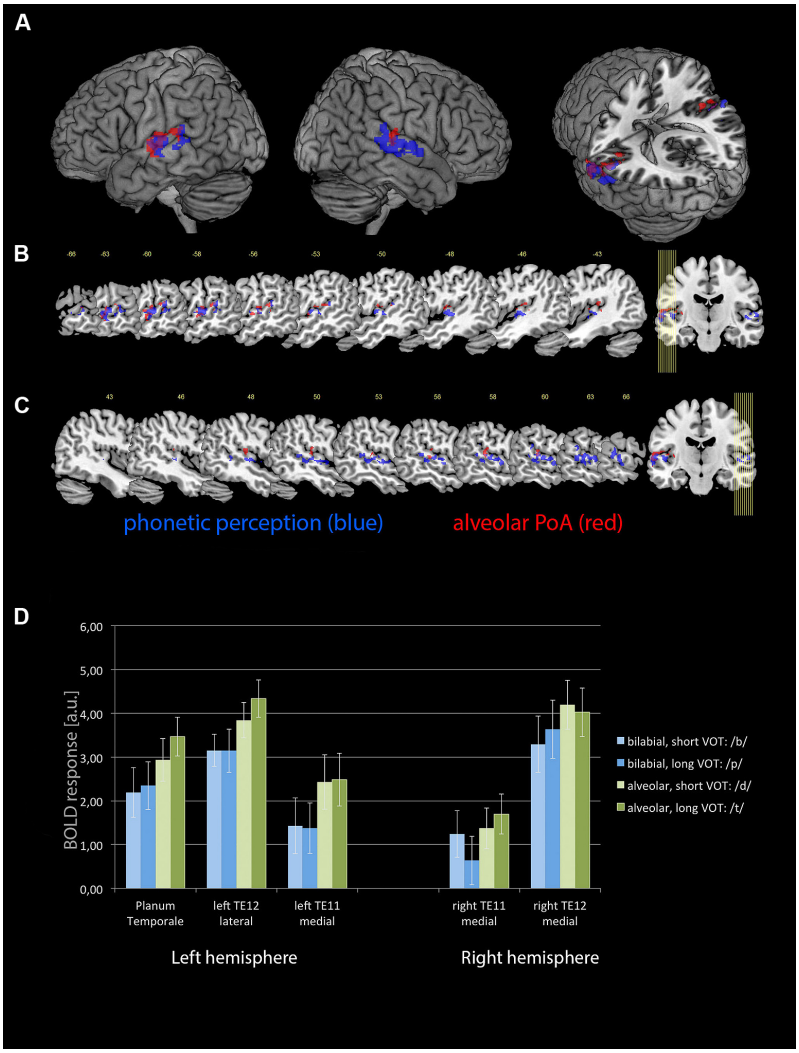


FIGURE 2 | The activations for the phonetic perception (blue) and specific additional activation for syllables with an alveolar PoA (red) as (A) render views as well as on a selection of sagittal slices for (B) the left hemisphere and (C) the right hemisphere. A voxel-wise threshold of $p < 0.001$ and a cluster threshold p(FWE) < 0.05 was applied to these statistical parametric maps. **(D)** BOLD responses (in arbitrary units) for each of the four different combinations of PoA and VOT, plotted for the medial cytoarchitectonic area TE1.1 and the later area TE1.2 of the left and right ACs (Morosan et al., 2001), as well as for the left PT. Error bars denote standard error.

to the phonetic stimulation occur. Alveolar CV syllables caused increased activation in the same areas as the phonetic stimulation, but stronger on the left side (see **Table 1** and **Figure 2**). In contrast, no additional effects were seen for the bilabial syllables. Furthermore, neither short nor long VOTs caused additional activations at the selected threshold. There was a marginally significant PoA × VOT interaction in medial aspects of the left AC, but only when the extent threshold was reduced to an uncorrected cluster size of $p < 0.05$, while keeping the peak threshold at $p < 0.001$. This interaction indicated that the activation was strongest for syllables with alveolar PoA and long VOT. Based on these results, five regions of interest were identified, with the following MNI coordinates: left lateral AC [−65 −12 3], left medial AC [−48 −15 6], left PT [−60 −34 15], right medial AC [50 −13 1], and right lateral AC [63 −22 7].

DYNAMIC CAUSAL MODELING

Dynamic causal modeling analyses were performed for the previously described regions of interest and a BMS analysis was applied to determine the most probable model. The winning model had a relative log-evidence of 280, and a posterior probability (pP) of pP = 1.0, with pP < 0.001 for the remaining 15 models. Finally, BMA was applied to determine the connection strength between the nodes. The overall connection matrix (A-matrix) demonstrated that all feedback connections from PT to the left and right ACs were inhibited when processing CV syllables, irrespective of PoA and VOT. The same pattern was observed for the connection from the left lateral AC to its right homolog. Finally, the B-matrix indicated that CV syllables with alveolar PoA inhibit the forward connectivity from the right lateral AC to PT (see **Figure 3**).

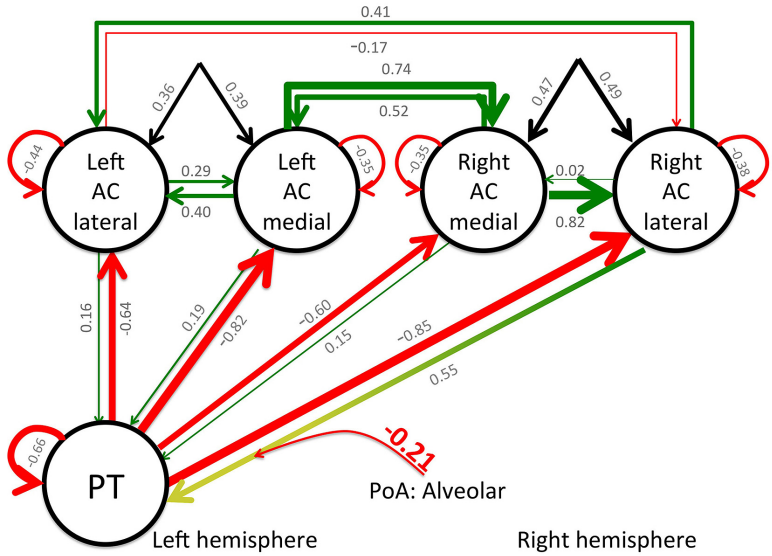


FIGURE 3 | Results of the DCM analysis: functional and effective connectivity as modeled by the winning model 3. Bayesian model averaging was applied to estimate the respective connection strength. Green lines indicate a positive connectivity, red lines inhibition, and the black lines indicate the input into the system. The values for the respective connectivity strength are printed in gray for the values from the A- and C-matrices and the red, bold value indicates the value from the B-matrix. To increase readability, the thickness of the lines indicates the respective connectivity strength, as well. Note that the presentation of a CV syllable that starts with an alveolar stop-consonant modulates the effective connectivity between the PT and the right lateral AC.

Since an effect for VOT was hypothesized, a corresponding DCM analysis was performed for VOT, although there was no significant effect for VOT in the voxel-wise analyses. In accordance with that, BMS did not favor a single model. However, two models had relatively high posterior probabilities ($pP > 0.4$). Both models had in common that the connection from the left lateral (model 1) or medial (model 2) AC to the respective homolog was increased. However, since neither the voxel-wise analysis nor the DCM analysis gave evidence for a systematic VOT effect, these results were not followed up.

FUNCTIONAL ASYMMETRY

The 2 × 2 × 2 × 2 repeated-measure ANOVA with the factor hemisphere, ROI, PoA, and VOT revealed significant main effects of PoA [$F(1,9) = 48.007$, $p < 0.001$] and ROI [$F(1,9) = 33.813$, $p < 0.001$], while the main effects for hemisphere and VOT became not significant (both $p > 0.3$). In addition, there was a significant PoA × hemisphere interaction [$F(1,9) = 10.049$, $p < 0.011$]. There were no other significant interaction effects. *Post hoc* tests, using Fisher LSD test, revealed that there was higher activity for alveolar syllables in the left than right hemisphere ($p < 0.0005$), and that alveolar syllables caused in both hemispheres higher activity than bilabial syllables (left hemisphere $p < 0.0001$, right hemisphere $p < 0.0001$). In contrast, the activity caused by bilabial syllables was not different between the left and right hemispheres ($p = 0.4$; see **Figure 2D**).

DISCUSSION

Using a within-speech design, where only CV syllables with different PoAs and VOTs were contrasted, the present study aimed to investigate the differential functional-asymmetry as well as modulation of the functional and effective connectivity as a function of PoA and VOT. To achieve this goal, this study depended on the superior sensitivity and high spatial resolution of a high-field 7 T MR scanner.

The results demonstrate that phonetic perception is a highly complex process that rests on the interaction and complementary processing properties of the left and right primary and secondary ACs. The overall phonetic perception revealed the expected pattern of bilateral activations within the left and right posterior temporal lobe, centred in the respective primary ACs. On this general level of phonetic perception, no strong functional asymmetry could be observed, as confirmed by the ROI analysis where no main effect of hemisphere was detected. However, syllables with an alveolar PoA increased the activation particularly in the left hemisphere, comprising the AC and extending posteriorly into PT. This was further confirmed by the ROI analysis, demonstrating the highest activation within TE1.1 and TE 1.2 of the left hemisphere for alveolar CV syllables. This result was paralleled with a decreased connectivity between the lateral right AC and the left PT. By contrast, neither short nor long VOT alone resulted in increased activations at the selected threshold, but an interaction of PoA and VOT was observed at a lower cluster extend threshold.

In general, these results indicate a context-dependent degree of lateralization on the level of the primary AC. This is further supported by three important results from the DCM analysis. First, all feedback connections from PT to the medial and lateral parts of the primary AC of the left and right hemisphere are inhibited during the perception of speech sounds, irrespective of PoA and VOT. Furthermore, the winning model indicated that the forward

connection from the right lateral AC to PT is inhibited during the processing of alveolar syllables, increasing the inhibitory influence of PT on the right lateral AC. Although the connectivity from the right medial AC to PT remained unchanged, the inhibition of the connection between the right lateral AC and PT may indicate that activity in PT has a suppressing influence on the activity in the right lateral AC. Supporting evidence for this interpretation comes from the ROI analysis, demonstrating only marginal activation differences between bilabial and alveolar CV syllables (see **Figure 2D**). In contrast, increased activity has been observed within the left AC and PT during the perception of alveolar CV syllables. Finally, the back connection from the left to the right lateral primary AC is generally inhibited during the processing of these syllables, which indicates a directed information flow from the right to the left lateral primary AC. Supporting evidence for this view comes from dichotic listening studies. Correlating diffusion tensor imaging data with dichotic listening performance, the connection strength between the left and right ACs determines the strength of the right ear advantage. A higher structural connectivity between the posterior superior temporal areas of both hemispheres cause a higher rate of correct left ear responses (Westerhausen and Hugdahl, 2008; Westerhausen et al., 2009a). The auditory commissures cross in the splenial region of the corpus callosum (Westerhausen et al., 2009a). Splenial lesions diminish the number of correct left ear responses in dichotic listening (Pollmann et al., 2002).

The presented DCM results support the view of a superior processing capacity of the left AC for spectrally complex sounds as opposed to the right AC that is assumed to process more tonal sounds, like vowels. However, the results also indicate a more differentiated view on this asymmetry, since the activation results, the ROI analysis, as well as DCM results demonstrate a functional asymmetry toward the left, particularly for the processing of syllables with an alveolar consonant. This speaks against a simple dichotomising of a left lateralized processing of consonants and a more right lateralized processing of vowels (cf. Rimol et al., 2006). The results rather suggest a constant and context depended variation of the functional asymmetry during speech perception, supporting the notion that the inherent acoustic complexity of speech sounds has to be taken more into account in studies of functional asymmetry (McGettigan and Scott, 2012). Moreover, the perception and decoding of speech signals has to be seen as an integrated interplay of the left and right auditory system across the theoretical concepts of consonants and vowels. In the present study, however, the analysis was averaged across vowels. Therefore, differential effects through co-articulation, that is the influence of the subsequent vowel on the articulation of the consonant, are eliminated, but future studies may focus on differential effects of co-articulation, as well.

Both the activation data and the DCM results support the known importance of PT in processing complex auditory information, such as speech signals (Binder et al., 1996; Griffiths and Warren, 2002; Price, 2012; Specht, 2014), although PT contribution has also been associated to auditory processing of non-verbal stimuli, spatial hearing, as well as auditory imagery (Binder et al., 1996; Specht and Reul, 2003; Specht et al., 2005; Obleser et al., 2008; Isenberg et al., 2012; Price, 2012). PT is an anatomical structure at the posterior end of the superior temporal gyrus, at the intersection with the parietal lobe. PT is typically larger on the left than on the right hemisphere (Binder et al., 1996; Preis et al., 1999; Dorsaint-Pierre et al., 2006), which was originally taken as evidence for a prominent role in speech perception- a view that has been revised toward a more general role in auditory processing (Griffiths and Warren, 2002; Krumbholz et al., 2005). Interestingly, intracranial recordings revealed categorical speech processing in the posterior superior temporal gyrus, including PT, when presenting a stimulus continuum that gradually varied PoA by changing between the voiced CV syllables /ba/ - /da/ - /ga/ (Chang et al., 2010). Concordantly, the current results confirm that PT could be seen as a computational hub for complex auditory processing that has not only a high sensitivity to speech sounds, but also presents a differential response and connectivity pattern to CV syllables with different PoA. The observed inhibitory effect of PT onto the right AC may therefore be a general process, not restricted to the processing of verbal sounds, but spectrally complex sounds *per se*.

The distinct contribution of lateral and medial aspects of the AC may reflect the different subfields of the AC, forming auditory field maps with orthogonal tonotopic and periodotopic gradients (Barton et al., 2012). Given the high spatial resolution and the high functional sensitivity of the applied method, the observed differential contribution of lateral and medial parts of the AC together with dominating right-to-left connectivity of the lateral AC, and higher medial-to-lateral connectivity within the right AC, may reflect the different contribution of these auditory field maps to the speech perception process (see **Figure 3**). Interestingly, there are no observed changes of any connectivity for the left AC, which possibly reflects its constant involvement in the processing of speech stimuli, while the right AC demonstrates a more context-dependent contribution.

In contrast to our *a priori* hypothesis, the present study could not detect a generally increased leftward asymmetry for syllables with a long VOT, irrespective of PoA. However, it should be emphasized that a trend toward a leftward asymmetry for long VOT syllables were observed at more liberal thresholds.

Finally, there are also limitations in the present study. First of all, ultra-high-field fMRI substantially increases the spatial resolution of fMRI and increases the temporal resolution to a certain extent, as well. However, these benefits are compromised by non-homogenous distribution of voxel values (Watanabe, 2012) and substantial susceptibility artifacts through ghosting and movement (Beisteiner et al., 2011), as well as image distortions, which have to be corrected (Chung et al., 2011). Often affected areas with reduced sensitivity to the BOLD signal are, for example, inferior parts of the temporal lobe. One has to bear in mind that possible activations in those areas may not have reached significance.

Second, one has to be cautious in generalizing these results to all languages, since different languages stress stop-consonants differently. However, it is still reasonable to assume that PoA

and/or VOT act as modulator of functional asymmetry in most languages.

In summary, all results are broadly in line with the notion that the left and right ACs demonstrate a division of labor in processing speech sounds. More specifically, we observed a varying pattern of functional left–right asymmetry that depended on the spectral complexity of the consonant sounds. Alveolar syllables generally caused a stronger activation of the left AC, including PT, as well as a reduced connectivity from the right lateral AC to the left PT, indicating a possible inhibitory effect of PT on the right AC during processing of spectrally more complex CV syllables.

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The effects of visual half-field priming on the categorization of familiar intransitive gestures, tool use pantomimes, and meaningless hand movements

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Although the control of meaningful gestures is one of the most left-lateralized functions, the relative contribution of the two hemispheres to their processing is still debated. We tested the effects of primes appearing in the left or right visual field in the form of pictures (Experiment 1), and words (Experiment 2) on categorization of movies showing intransitive ("communicative") gestures, tool use (transitive) pantomimes, and meaningless movements. Fifteen participants (eight women) watched 36 movies (12 from each category) primed for 150 ms with either a congruent or incongruent stimulus followed by a 50-ms mask. On congruent trials, a picture or word was directly related to the presented gesture, including nonsense pictures or non-words for meaningless actions. On incongruent trials, a picture or word belonged to a different category. In Experiment 1, intransitive gestures were categorized significantly faster than the other two types of hand movements. Moreover, whereas the categorization of transitive gestures was significantly facilitated by congruent pictures on the right, the effect was weaker for intransitive, and reversed for meaningless movements. In Experiment 2, intransitive gestures were again categorized significantly faster, but transitive significantly slower than the other two gesture categories. Yet, there was now a significant facilitation of intransitive, and inhibition of transitive gesture categorization following congruent prime words in the right visual field, and significantly faster categorization of intransitive gestures following incongruent words in the left visual field. These outcomes lend support to the complexity account of differences in left-hemisphere representations of meaningful gestures reported in the neuropsychological, behavioral, and neuroimaging literature. Nevertheless, they also indicate that the representations of intransitive gestures show some differential, and sometimes counterintuitive sensitivity to right hemisphere processing.

Keywords: intransitive gestures, tool use pantomimes, meaningless actions, categorization, priming, pictures, words, representation

INTRODUCTION

Our current knowledge on the laterality of representations underlying meaningful gestures comes primarily from research on patients with acquired brain injuries, and more recently from experiments using functional neuroimaging (for reviews, see Frey, 2008; Rumiati et al., 2010; Goldenberg, 2013a; see also Goldenberg, 2013b; Króliczak, 2013a). These studies overwhelmingly point to the left hemisphere as the seat of the control of gesture. Yet, in the majority of these projects the emphasis was put primarily on manual performance, e.g., the planning and subsequent execution of conventionalized hand movements based on verbal commands, or the quality of imitation of the just seen meaningful vs. meaningless actions. Therefore, substantially less is known about the laterality of neural mechanisms involved in recognition, or even a potentially easier process of the categorization of skilled gestures (cf. Rumiati et al., 2010; pp. 224–225).

Among the gestures whose specific representations have been extensively explored and debated are sequential hand movements and/or postures frequently used in everyday communication, which are referred to as *intransitive gestures* (e.g., waving goodbye, beckoning, or hitchhiking), and less frequently used object-related *transitive actions* often referred to as *tool use pantomimes* (e.g., simulated use of a hammer, scissors, or a key). Of course, counter to transitive or tool use actions, the former gestures do not require real or imagined objects to convey their meaning. Yet despite these differences, empirical evidence in favor of independent (dissociable) mechanisms for the two types of gestures is inconclusive. On the one hand, patients with apraxia have been found either less impaired during performance of familiar intransitive gestures (Roy et al., 1991; Foundas et al., 1999; Haaland et al., 2000; cf. Mozaz et al., 2002) or not affected at all following left hemisphere lesions, despite showing considerable impairments during tool use pantomime (Rapcsak et al., 1993; Dumont et al., 1999, see also Stamenova et al., 2010). At first glance, then, such neuropsychological data suggest that the neural representations of transitive skills are lateralized more to the left hemisphere. Alternatively, the left hemisphere may support

independent mechanisms for transitive and intransitive skills, with a possible extension of the processing of the latter to the right hemisphere. On the other hand, recent neuroimaging and behavioral evidence (Carmo and Rumiati, 2009; Kroliczak and Frey, 2009; see also Mozaz et al., 2009; Króliczak, 2013b) indicates that tool use pantomime and imitation may simply place higher demands on a common representational system mediating both intransitive and transitive manual skills, a system with close ties to language functions (Kroliczak et al., 2011; for a review, see Króliczak, 2013a).

Whether independent, for example differently lateralized, or rather common mechanisms are also involved in the visual processing (i.e., perception or recognition) of the two gesture categories is even more inconclusive. The reports from recent functional neuroimaging studies that directly addressed this question (Villarreal et al., 2008; Króliczak, 2013b) indicate that bilateral networks of areas are engaged during watching of both intransitive and transitive actions. The most striking difference was such that in the former project a greater involvement for perception of intransitive gestures was observed in a left-hemisphere structure located within a common network, specifically in the left inferior frontal gyrus (which was also engaged by transitive gestures but to a lesser degree). In the latter project, conversely, a greater and some bilateral involvement was observed for the perception of transitive actions, and only in areas that were outside of the common network of activation mediating both gesture categories (which may, arguably, reflect some dissociable mechanisms). Furthermore, whereas Villarreal et al. (2008) linked the greater left inferior frontal activity to the recognition of semantic content conveyed by their symbolic intransitive gestures, Króliczak (2013b) linked the observed increases of activity to the need for deeper visual encoding and more complex visuo-spatial transformations required for the processing of transitive (tool use) pantomimes. A preliminary conclusion that can be drawn from these two studies is such that the mechanisms mediating gesture categorization and/or recognition might be organized and/or lateralized somewhat differently from the mechanisms underlying their skilled performance.

In order to shed some new light on the above-mentioned controversies and arguments, in this study we tested (1) whether or not the potential differences in the familiarity and/or complexity between intransitive and transitive gestures are also evident in accuracy and response times accompanying their categorization, (2) whether or not the representations of the two gesture categories show different sensitivity to lateralized visual and linguistic cues, and if there are no clear hints of dissociable mechanisms, (3) whether or not the categorization of meaningful gestures differs from that of the processing of meaningless actions (that we used in this study as a control condition).

If intransitive gestures are indeed easier to categorize, this should be reflected at least in shorter response times. Moreover, if representations of the two gesture categories show different sensitivity to visual and semantic cues, and/or they are differently organized in the brain, we should observe distinct effects of such cues on their categorization (e.g., facilitation or inhibition of response times), possibly modulated by the side where the cues are presented. In particular, whereas congruent cues were expected to facilitate categorization mainly when projected first to the hemisphere specialized in processing of a particular gesture type, incongruent cues were expected to interfere most when projected to this same hemisphere, and their influence could be much weaker—but perhaps comparable with congruent cues—when reaching the less specialized hemisphere first. Finally, we also expected that the pattern of response times for the categorization of meaningless hand movements, that have no prior representation in the brain, would not resemble the patterns observed for meaningful gestures.

EXPERIMENTS

Although the order of the two experiments described here—one with pictures, and one with words as primes—was counterbalanced across the whole sample of subjects, for simplicity we will nevertheless refer to the use of pictures as Experiment 1, and the use of words as Experiment 2. The two experiments were carried out in *Action and Cognition Laboratory* in the Institute of Psychology at Adam Mickiewicz University in Poznań, Poland. Participants took no longer than 22 min to complete the whole study. Approved by the local Ethics Committee, this research was performed in accordance with principles of the Helsinki 1964 Declaration.

Seventeen volunteers partook in this research after giving their informed consent. The results from two participants (two women) were excluded from further analyses because of low accuracy (56.1%, with the average accuracy of 82% and $SD = 8.5$ in both studies) or the low number of the recorded responses (2%) due to an equipment malfunction.

EXPERIMENT 1: CATEGORIZATION OF GESTURES PRIMED BY PICTURES

Methods

All 15 healthy volunteers (eight women, mean age = 23.0; $SD = 1.5$) who contributed to this research had normal or corrected-to-normal visual acuity, and were native speakers of Polish. Although handedness was not measured with a questionnaire, before the study participants explicitly declared which hand they typically use in daily activities such as writing, throwing, and using a spoon. The vast majority of subjects (13) were right-handed. (The RT patterns of two left-handed individuals were indistinguishable from those of right-handers, most likely because similarly to the majority of left-handers they had praxis and language typically lateralized; see Kroliczak et al., 2011).

Before the experiment proper, subjects participated in a short pre-training phase composed of trials containing two movies from each of the to-be-tested category. Although the trial structure was the same, the videos used were recorded on a different occasion with a different background. It was during this introduction to the study that participants were asked for the first time to fixate the cross in the middle of the screen throughout the study. As confirmed by the experimenter, they were indeed able to maintain fixation when the priming pictures were shown, which is critical for this paradigm.

Participants were seated 57 cm in front of the computer monitor, which subtended the visual angle of $30 \times 18.5°$. Thirty six centrally presented short videos showing gestures performed by an actor were used as target stimuli. Only the right arm and hand,

chest and the right upper leg were visible on the screen, whereas the face and most of the left side of the body remained outside of the frame. The recorded movements belonged to three categories: intransitive ("conversational"), transitive (simulated tool use) gestures, and meaningless hand movements, with 12 videos in each category. The list of all 24 meaningful gestures can be found in the Appendix. The movies were recorded with BENQ DC C1060 camera located 1.6 meters in front of the actor.

In Experiment 1, the to-be-categorized hand movements shown in the videos were primed by: (1) pictures of hands in postures that were most characteristic for intransitive gestures used in this study, (2) pictures of tools whose usage was pantomimed in the clips, or (3) by meaningless pictures (obtained with a polar-coordinate filter distorting the images from the intransitive and transitive categories to make them unrecognizable; e.g., in Photoshop: go to Filter, choose Distort, then Polar Coordinates, then Rectangular to Polar. For many objects the function had to be used at least twice to make them beyond recognition.). Due to differences in typical orientations of hand postures and objects, and/or sizes of objects, the pictures projected either 4×4 or $3 \times 3.5°$ of visual angle (with the different sizes of priming stimuli distributed equally across the three categories of trials, and their center of gravity kept in the same spot). The stimuli were shown on a gray background (RGB 250/250/250), and were preceded by a fixation point, i.e., a black cross in the middle of the screen.

The trial structure was as follows: the fixation cross alone was shown for a variable interval of 1000, 1500, or 2000 ms (thus introducing some uncertainty about the timing of the following events). Then, a prime stimulus appeared for 150 ms either on the left or right side of the screen (ca. 7° of visual angle from the fixation point), and was immediately masked for 50 ms with a checkerboard pattern, which always subtended the visual angle of $4 \times 4°$. (All the volunteers were explicitly instructed to maintain fixation on a central cross even if there is an additional stimulus briefly shown to the right or left of the cross.) Subsequently a movie was presented and it remained on the screen until a response was provided or for up to 4 s. Participants were asked for categorization of the watched gestures as representing: "conversation" (intransitive), "tool" (transitive), or "nonsense" (meaningless gesture). If the answer was not given (by pushing an appropriate button), the next trial started 1 s after the end of the video. The trial structure is depicted in **Figure 1**.

The target videos were preceded either by congruent or incongruent primes. In the former case, the prime belonged to the same category as the video (e.g., the characteristic hitch-hiking hand posture preceded the hitch-hiking gesture, a picture of a hammer preceded a movie showing a pounding gesture, or an unrecognizable image preceded a meaningless movement). In the case of incongruent primes, the stimuli belonged to a category different from the main stimulus (e.g., a picture of a hammer shown before the hitch-hiking or a meaningless gesture). Each movie appeared only three times during the course of a given experiment, and it was preceded by a prime belonging to each category. For that reason, half of the randomly selected movies in a given category were preceded by congruent primes on the left, and the remaining half by congruent primes on the right. In the case of incongruent primes—which now belonged to two different categories—for half of the randomly selected movies all the randomly assigned incongruent primes appeared on the left, and for the remaining half of the movies all the assigned primes appeared on the right. By doing this we made sure that prime location was also properly counterbalanced in each participant (not for each movie, but definitely for the whole category of movies). The order of trials was randomized differently for each participant and it was divided into three blocks, 36 trials each. There was an optional break after block one, and a compulsory break (lasting at least 1 min) after block two.

The design was implemented in SuperLab ver. 4.5.2 (Cedrus®, San Pedro, CA), and carried out with the use of Dell *Latitude D620* PC. "RB-530" response pad by Cedrus was used for measuring accuracy and response times. The patterns of responses were counterbalanced across hands and gesture types. Namely, when the left button of the pad was pressed with the left-hand fingers for intransitive gestures, the button on the right was pressed with the right-hand fingers for transitive gestures, and vice versa. For meaningless gestures participants always pressed the middle button with either their right- or left-hand fingers.

All the collected data were analyzed with two separate repeated-measures *Analyses of Variance* (*ANOVAs*), one for accuracy and one for response times to correctly categorized gestures. The within-subject factors were *gesture* (intransitive, transitive, meaningless), *prime location* (left, right), and *prime type* (congruent, incongruent). The adopted level of significance was $p < 0.05$. If necessary, the required *post-hoc* tests were Bonferroni corrected (marked as Bf-p). For reaction times accompanying a correct categorization of movies, outliers greater than two standard deviations above or below the mean (calculated across conditions, less than 1% of all trials) were removed.

Results

Recognition accuracy. Because none of the differences between the categorization accuracy for intransitive and transitive gestures was significant (neither in the main effects nor the interactions, often even without the necessary Bonferroni correction), these data will not be discussed at length here. Except for the main effect of gesture [$F_{(2,\ 28)} = 8.1$, $p < 0.01$; Partial Eta Squared ($_p\eta^2$) = 0.37; observed power (alpha) = 0.94] such that both intransitive and transitive gestures were categorized with significantly greater accuracy than meaningless hand movements (Bf-$p < 0.01$, and Bf-$p < 0.05$, respectively), all the remaining significant main effects and interactions were driven by differences in the categorization of meaningless actions. (These are of no particular interest in the absence of significant differences between the two meaningful gesture categories.) The average categorization accuracy for intransitive gestures was 83% (SE = 2%), for transitive gestures it was 85% ($SE = 2.8\%$), and for meaningless hand movements it was only 73% ($SE = 1.7\%$).

Response Times (RTs) for correctly categorized gestures. There was a main effect of *gesture* [$F_{(2,\ 28)} = 96.6$, $p < 0.001$; $_p\eta^2$ = 0.87; alpha = 1.0] such that intransitive gestures were categorized significantly faster than the other two types of hand movements (mean RT for intransitive = 1479 ms, $SE = 40$ ms; transitive = 1906 ms, $SE = 50$ ms; and meaningless = 1867 ms,

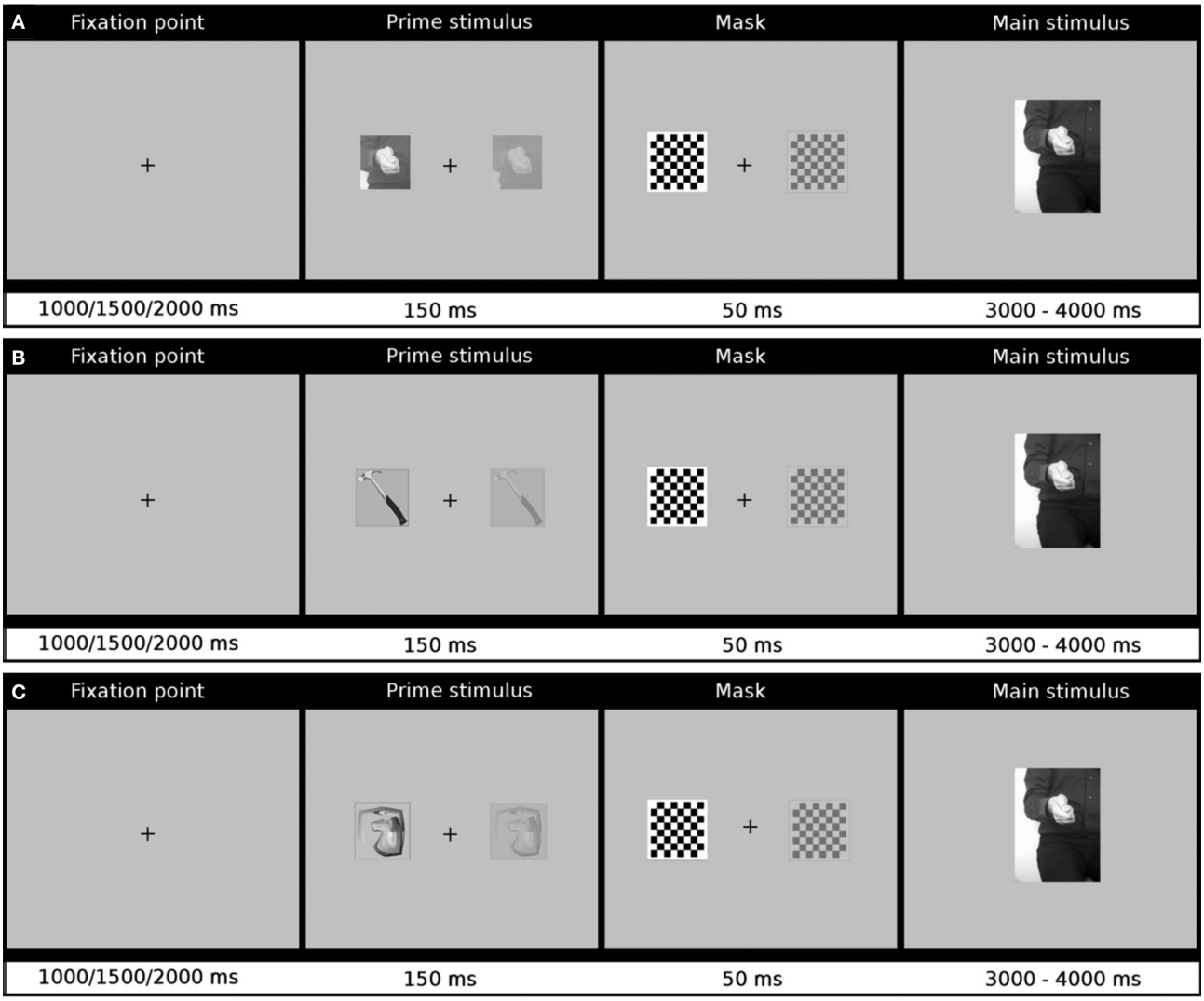


FIGURE 1 | Trial structure and timing. In **(A)** the priming stimulus was a characteristic hand posture, in **(B)** it was a picture of a tool, and in **(C)** an image of a distorted, unrecognizable object. After a fixation point presented on a blank screen for a variable time interval (1000, 1500, or 2000 ms), the priming stimulus was shown either on the left or right (as shown by a grayed inset) for 150 ms, followed by a 50-ms mask, and a centrally presented gesture. The movie stayed on the screen until a participant responded or for up to 4 s. Additional 1-s delay interval was introduced after a movie disappeared.

$SE = 63$ ms; Bf-$p < 0.001$ in both cases). No significant difference was observed between transitive and meaningless gestures (uncorrected $p = 0.8$). This effect is shown in **Figure 2**. There was also a main effect of *prime type* [$F_{(1,\ 14)} = 16.1$, $p < 0.001$; ${}_p\eta^2 = 0.53$; alpha $= 0.96$] such that movies preceded by a congruent prime were categorized significantly faster than on incongruent trials (mean RT for congruent $= 1727$ ms, $SE = 49$ ms vs. incongruent $= 1775$ ms, $SE = 47$ ms). The effect of prime location was not significant [$F_{(1,\ 14)} = 0.23$, $p = 0.6$; ${}_p\eta^2 = 0.02$; alpha $= 0.07$].

Importantly, there was a significant interaction between *gesture* and *prime location* [$F_{(2,\ 28)} = 37.8$, $p < 0.001$; ${}_p\eta^2 = 0.73$; alpha $= 1.0$], such that intransitive and transitive gestures were categorized significantly faster when they were primed by a stimulus in the right visual half field (VHF), as compared to the left VHF (Bf-$p < 0.01$ and Bf-$p < 0.001$, respectively). For meaningless gestures the effect was reversed (Bf-$p < 0.001$). There was also a significant interaction between *prime location* and *prime type* [$F_{(1,\ 14)} = 7.5$, $p < 0.01$; ${}_p\eta^2 = 0.35$; alpha $= 0.72$], but the effect of congruent primes leading to faster categorization only when they were presented in the right VHF turned out to be insignificant after the Bonferroni correction (Bf-$p = 0.06$). Left-sided priming had an even weaker effect in this interaction (uncorrected $p = 0.07$). Nevertheless, all these results should be interpreted with caution because there was also a very intuitive and significant three-way interaction [between *gesture*, *prime side*, and *prime type*; $F_{(2,\ 28)} = 5.3$, $p < 0.01$; ${}_p\eta^2 = 0.28$; alpha $= 0.80$]. Follow up tests of simple main effects were used to clarify the straightforward relations of these factors. The tests revealed that intransitive gestures tended to be categorized faster

when preceded by congruent primes on the right, but this effect did not survive Bonferroni correction for multiple comparisons. Nevertheless, the impact of right-sided congruent priming on their categorization was revealed by a planned *a priori* *t*-test [$t_{(14)} = 2.6$; $p < 0.05$]. The effect of incongruent primes on the categorization of intransitive gestures was even weaker (Bf-$p = 0.2$). A significant facilitation of response times by congruent right VHF primes was observed for transitive gestures (Bf-$p < 0.001$), but not for incongruent primes (uncorrected $p = 0.44$). A completely reversed effect of primes, i.e., response facilitation when they were presented in the left VHF, and more importantly, regardless of their congruency, was observed for meaningless gestures (Bf-$p < 0.01$, and Bf-$p < 0.001$, respectively, on congruent and incongruent trials). These effects are shown in **Figure 3**. The mean response times, as well as mean accuracy data, for all the conditions are listed in **Table 1**.

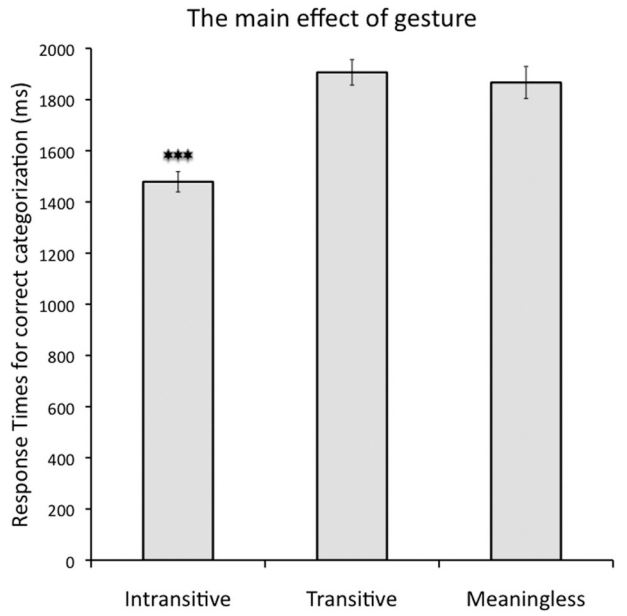


FIGURE 2 | The main effect of gesture for correctly categorized movies when pictures were used as primes. Intransitive gestures were categorized significantly faster than transitive and meaningless movements. Response times for the latter two did not differ between each other. Asterisks indicate a difference with Bonferroni-corrected *p*-value of 0.001 (***).

Discussion of Experiment 1

Intransitive ("*conversational*," non-object related) gestures were categorized significantly faster than transitive (simulated tool use) gestures and meaningless hand movements, whose categorization efficacy—in terms of response times—did not differ between each other. Such an outcome is consistent with an earlier observation that, at least under time pressure, healthy individuals also perform poorer during imitation of transitive actions, irrespective of whether they are meaningful or meaningless (Carmo and Rumiati, 2009). Slower performance with transitive, as well as slower and poorer categorization of meaningless gestures in our study, is therefore consistent with an idea that tool use pantomimes and nonsense hand movements, perhaps mainly due to greater movement complexity, are harder to process than more familiar intransitive gestures (Vingerhoets, 2008; Kroliczak and Frey, 2009; Króliczak, 2013b; see also Johnson-Frey et al., 2005 and Villarreal et al., 2008, where meaningless hand movements were used in a control condition). It must be emphasized, though, that the pattern of response times for correctly categorized gestures observed in our study is exactly the opposite of what was found in an fMRI report by Villarreal et al. (2008), where both the

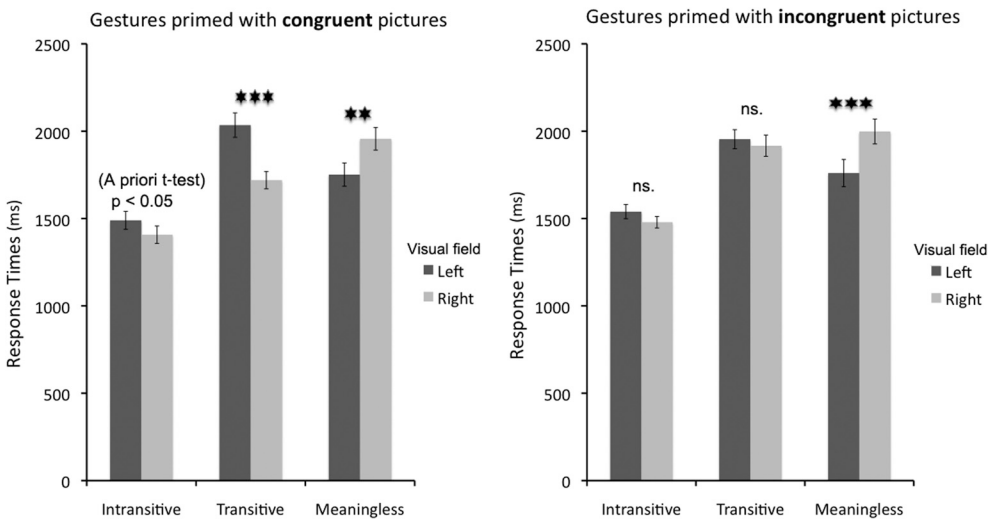


FIGURE 3 | Response times to correctly categorized intransitive gestures, tool use pantomimes, and meaningless hand movements primed by congruent or incongruent pictorial cues presented in the right or left visual field. Transitive gestures were greatly facilitated by congruent pictorial cues on the right, and intransitive gestures showed a similar trend. The effect for meaningless movements was reversed. Incongruent pictorial cues had no effect on categorization of both meaningful gesture types, but the effect for meaningless movements was in the same direction as before. Asterisks indicate differences with Bonferroni-corrected *p*-values of at least 0.01 (**), or 0.001 (***).

Table 1 | Pictures as primes—Experiment 1.

Trial type			Response time (ms)	St. error	Accuracy (%)	St. error	*N*
Intransitive	Left	Congruent	1490	51	77.3	3.3	15
		Incongruent	1540	40	87.4	3.0	15
	Right	Congruent	1407	49	87.5	3.9	15
		Incongruent	1479	32	80.3	2.6	15
Transitive	Left	Congruent	2035	69	90.5	3.3	15
		Incongruent	1954	54	87.6	3.2	15
	Right	Congruent	1720	49	73.3	4.2	15
		Incongruent	1917	61	86.3	3.9	15
Meaningless	Left	Congruent	1751	66	61.6	4.0	15
		Incongruent	1760	77	96.0	1.9	15
	Right	Congruent	1956	64	54.9	2.9	15
		Incongruent	1998	71	77.3	4.6	15

Gesture type (intransitive, transitive, meaningless), prime location (left, right), prime type (congruent, incongruent) with their mean response times (ms), accuracy (%), and their standard errors of the means, for Experiment 1 with pictures serving as primes are listed.

recognition of transitive and meaningless actions was significantly faster (uncorrected for multiple comparisons) than the recognition of movements belonging to an intransitive category. Yet, the testing paradigm they used was substantially different from ours.

One can speculate that the categorization of such well-known gestures as "*waving hello*" or "*hitchhiking*" may be rather automatic and less dependent on "contextual" pictorial cues, in contrast to meaningless movements, or even tool use gestures, which can be more difficult to decipher when seen unexpectedly. This hypothesis, combined with the issue of laterality of their representations (or processing) was tackled by analyzing the effects of *prime side* and *prime type*. Although the processing of transitive (tool use) gestures was slower, and comparable to meaningless movements, their categorization profited most from congruent pictures presented briefly on the right. Such an effect could either indicate that this gesture category is most strongly left lateralized or that it is particularly sensitive to relevant pictorial cues when they are processed in the left hemisphere. (Of course, this effect could also indicate a combination of both left-sided representations of tool use skills and their particular responsiveness to pictorial cues). The most efficiently categorized intransitive gestures, on the other hand, were not facilitated as much by congruent pictures on the right. This could be due to (1) a floor effect, such that one cannot simply get much faster with their categorization; (2) the fact that even the most characteristic hand postures depicted in the priming stimuli are more difficult to process than pictures of tools (which do a very good job of priming the categorization of transitive gestures), or (3) weaker laterality of representations mediating intransitive skills (e.g., Rapcsak et al., 1993; Dumont et al., 1999). Indeed, the idea that intransitive and transitive skills might be mediated by different mechanisms—with intransitive gestures being supported more strongly by the right hemisphere, or more bilaterally, i.e., by both hemispheres—figures rather prominently in most influential theories of praxis and inspires research and discussions on representations of praxis skills up until today (e.g., Rothi et al., 1991; Cubelli et al., 2000; Buxbaum, 2001; Króliczak, 2013b; see also Binkofski and Buxbaum, 2013).

Incidentally, neither the categorization of intransitive nor transitive gestures was influenced by incongruent primes, irrespective of their presentation side. Conversely, response times accompanying correct decisions on meaningless hand movements were facilitated by priming stimuli on the left, whether congruent or incongruent. Because postulating their explicit representations in one of the two hemispheres does not make much sense, it stands to reason that the categorization of such unskilled actions (i.e., movements which are not in a repertoire of our manual skills) may depend more on visuo-spatial abilities, and more deliberate processing, often associated with the right cerebral cortex (e.g., Kroliczak et al., 2007; cf. Kroliczak et al., 2008; see also Whitehouse and Bishop, 2009; Rossit et al., 2011). For these two reasons alone, the categorization of meaningless movements would be less affected by the meaning of the priming cues. In short, the observed response facilitation might be due to an engagement of related right hemisphere processing before the meaningless action is encountered.

The results so far are consistent with a long-standing idea that tool use skills are represented in the left hemisphere (see also Vingerhoets et al., 2009; Verma and Brysbaert, 2011; Garcea et al., 2012; Vingerhoets et al., 2012), whereas meaningless actions might be primarily or preferentially processed in the right hemisphere. (This is probably one of the reasons why meaningless actions make a good control condition in fMRI projects on gestures.) The status of intransitive or "communicative" gestures is less obvious because either they have more bilateral representations or are simply less dependent on the context in which they are encountered. The latter two ideas can be explored by changing the primes from pictorial to linguistic cues, and this is exactly what has been done in Experiment 2.

If intransitive gestures are represented more bilaterally, there should be no substantial facilitation from priming of these actions by closely related verbal cues presented in the right visual field (i.e., processed immediately by the left hemisphere). Moreover, one could even observe a significant interference in the form of slowing down of their categorization by incongruent words presented in the left visual field (i.e., engaging initially the right hemisphere).

EXPERIMENT 2: CATEGORIZATION OF GESTURES PRIMED BY WORDS

Methods

These same 15 healthy volunteers [eight women, mean age = 23.0 ($SD = 1.5$) years of age] were involved in this study. The methods used were very similar to Experiment 1, except for the primes. Namely, the videos were now preceded by briefly presented (150-ms) linguistic cues, i.e., single words or brief two-word expressions most often associated with intransitive and transitive gestures (including their names, and object names), or meaningless strings of letters. Again, the priming stimuli were either congruent (i.e., belonged to the same category) or incongruent

with the target gesture (i.e., represented the other two categories). All these primes were also immediately masked (for 50 ms) with a string of nine hashes (###. . .) which exceeded the longest of the priming cues by one symbol. The font size used both for words and non-words was 26 pt, whereas that for the mask was 28 pt. Thus, given that our priming cues consisted of 2–8 characters, they subtended the visual angle from 0.7 to 3°. The stimuli of various sizes were distributed more or less equally across all the conditions.

The relevant words or expressions related to meaningful gestures that were shown in the videos were chosen from the most frequent responses provided before the study by five student volunteers (two women) who did not participate, and were not involved in any way, in this research project.

Similarly to Experiment 1, the collected data were analyzed with two separate repeated-measures *ANOVAs*, for accuracy and for response times to correctly categorized gestures. Again, the within-subject factors were *gesture* (intransitive, transitive, meaningless), *prime location* (left, right), and *prime type* (congruent, incongruent). The adopted level of significance was $p < 0.05$ and, if necessary, *post-hoc* tests were Bonferroni corrected (Bf-p). For RTs to correctly categorized movies, outliers greater than two standard deviations above or below the mean were removed (less than 1% of all trials).

Results

Recognition accuracy. Similarly to Experiment 1, there was a main effect of gesture [$F_{(2,\ 28)} = 4.8$, $p < 0.05$; ${}_p\eta^2 = 0.25$; alpha = 0.75] but now it was such that only intransitive gestures were categorized with significantly greater accuracy than meaningless hand movements (Bf-$p < 0.05$), whereas the difference between transitive and meaningless actions did not reach significance level (Bf-$p = 0.2$). Intransitive and transitive gesture categorization was comparable (Bf-$p = 1.0$). There was also a counterintuitive main effect of *prime location* [$F_{(1,\ 14)} = 10.0$, $p < 0.01$; ${}_p\eta^2 = 0.42$; alpha = 0.84], such that gestures primed by a word in the left visual field were categorized with greater accuracy than gestures primed by a word in the right visual field, and this effect mirrors the one observed for RTs (see below). Although there was also a significant interaction between *gesture* and *prime type* [$F_{(2,\ 28)} = 7.6$, $p < 0.01$; ${}_p\eta^2 = 0.35$; alpha = 0.92], none of the differences between categorization accuracy for any gestures was significant when Bonferroni correction was applied. There were no other significant effects. The average categorization accuracy for intransitive gestures was 87% ($SE = 1.9\%$), for transitive gestures it was 85% ($SE = 2.5\%$), and for meaningless hand movements it was only 76% ($SE = 3.1\%$).

RTs for correctly categorized gestures. There was a main effect of *gesture* [$F_{(2,\ 28)} = 133.0$, $p < 0.001$; ${}_p\eta^2 = 0.91$; alpha = 1.0] such that similarly to Experiment 1 intransitive gestures were again categorized significantly faster (mean $RT = 1453$ ms, $SE = 42$ ms) than transitive gestures (mean $RT = 1985$ ms, $SE = 47$ ms; Bf-$p < 0.001$) and meaningless hand movements (mean $RT = 1854$ ms, $SE = 49$ ms; Bf-$p < 0.001$). Importantly, counter to Experiment 1, transitive gestures were categorized significantly slower than meaningless movements (Bf-$p < 0.05$). This effect is shown in **Figure 4**. In sharp contrast to Experiment 1, a main effect of *prime location* was now significant [$F_{(1,\ 14)} = 27.6$, $p < 0.001$; ${}_p\eta^2 = 0.66$; alpha = 0.99], but it was also quite unexpected, such that the studied gestures were categorized significantly faster when the priming stimuli were presented in the left VHF (mean $RT = 1736$ ms, $SE = 41$ ms) as compared to the right VHF (mean $RT = 1793$ ms, $SE = 43$ ms). Finally, there was also a counterintuitive main effect of *prime type* [$F_{(1,\ 14)} = 6.3$, $p < 0.05$; ${}_p\eta^2 = 0.31$; alpha = 0.64] with gesture categorization being significantly faster following incongruent primes (mean $RT = 1743$ ms, $SE = 44$ ms) as compared to congruent primes (mean $RT = 1785$ ms, $SE = 40$ ms). The latter two main effects should not be overrated, though, given the significant interactions that were also obtained.

The first significant interaction was between *gesture* and *prime location* [$F_{(2,\ 28)} = 18.6$, $p < 0.001$; ${}_p\eta^2 = 0.57$; alpha = 1.0]. This effect was such that intransitive gestures were categorized significantly faster following priming words on the right (Bf-$p < 0.01$), whereas transitive gestures were categorized significantly faster following priming words on the left (Bf-$p < 0.001$). The effect of prime location for meaningless hand movements was similar to transitive gestures but turned out to be insignificant after Bonferroni correction (uncorrected $p = 0.04$). There was also a significant interaction between *prime location* and *prime type* [$F_{(1,\ 14)} = 12.9$, $p < 0.01$; ${}_p\eta^2 = 0.48$; alpha = 0.92]. This interaction, on the other hand, suggested that gesture categorization was significantly slower when the right-sided priming words were actually congruent (Bf-$p < 0.01$), whereas the left-sided words had no effect whatsoever (uncorrected $p = 0.37$). As in

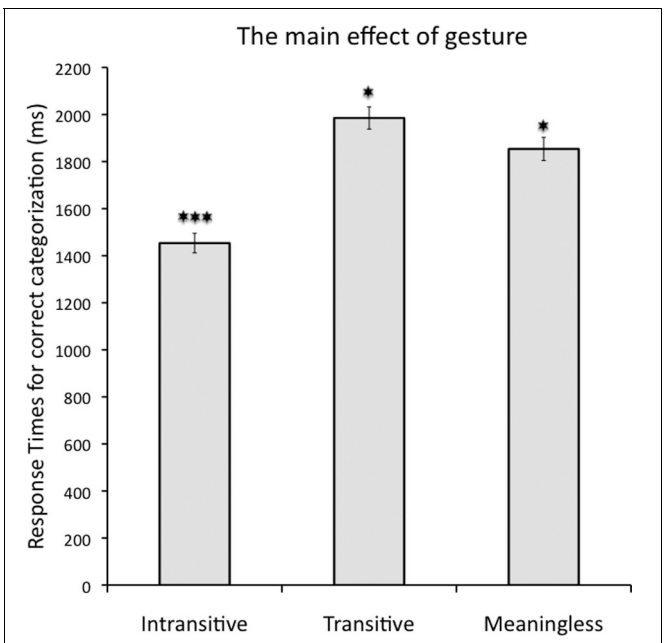


FIGURE 4 | The main effect of gesture for correctly categorized movies when words were used as primes. Intransitive gestures were again categorized significantly faster than transitive and meaningless movements. Response times for the latter two now also differed between each other. Asterisks indicate differences with Bonferroni-corrected *p*-values of 0.05 (*), or 0.001 (***).

Experiment 1, all the above effects, including the two 2-way interactions, should be interpreted with great caution because there was also a much more intuitive significant three-way interaction between *gesture*, *prime side*, and *prime type* [$F_{(2,\ 28)} = 54.0$, $p < 0.001$; ${}_p\eta^2 = 0.79$; alpha = 1.0]. Similarly to Experiment 1, tests of simple main effects were utilized to clarify the apparently complex relationships between these factors. The tests revealed that intransitive gestures were categorized significantly faster when primed by congruent words on the right (as compared to congruent words on the left; Bf-$p < 0.001$), whereas their categorization was significantly slower when primed by incongruent words on the right (as compared to incongruent words on the left; Bf-$p < 0.001$). In sharp contrast, for both transitive gestures and meaningless hand movements the effect of *prime type* was reversed because their categorization was significantly slower when congruent cues appeared on the right (as compared to congruent cues on the left; Bf-$p < 0.001$ in both cases), whereas there was no impact of incongruent priming words on their categorization that could be related to the presentation side (uncorrected $p = 0.19$ for transitive, and $p = 0.09$ for nonsense movements). These effects are shown in **Figure 5**. The mean response times, as well as mean accuracy data, for all the conditions from Experiment 2 are listed in **Table 2**.

Finally, for clarification of the obtained interaction effects, two additional *post-hoc* tests are described here to compare response times accompanying correct categorization of intransitive gestures following incongruent linguistic cues on the left with the effects of congruent cues on the right, and the impact of congruent cues on the left. Both of the observed differences were significant (Bf-$p < 0.001$ in both cases). Namely, although the categorization of intransitive gestures following incongruent cues on the left was significantly slower as compared to the effects of congruent cues on the right, it was at the same time significantly faster when compared to the effects of congruent cues on the left. This effect is shown in **Figure 6**. In other words, for the categorization of intransitive gestures, taking into account a valid cue from the left visual field requires significantly more time than a rejection of an invalid cue. (Of course, an observation that categorizing these gestures is faster following incongruent words on the left as compared to incongruent words on the right has

Table 2 | Words as primes—Experiment 2.

Trial type			Response time (ms)	St. error	Accuracy (%)	St. error	*N*
Intransitive	Left	Congruent	1628	53	97.3	1.8	15
		Incongruent	1399	43	90.5	1.7	15
	Right	Congruent	1265	38	79.9	4.4	15
		Incongruent	1521	47	82.3	3.8	15
Transitive	Left	Congruent	1789	43	84.4	6.0	15
		Incongruent	1971	47	89.4	3.0	15
	Right	Congruent	2266	85	78.9	3.0	15
		Incongruent	1914	56	87.8	2.7	15
Meaningless	Left	Congruent	1754	58	84.4	4.1	15
		Incongruent	1872	58	73.9	3.6	15
	Right	Congruent	2008	56	75.6	3.6	15
		Incongruent	1782	56	70.1	4.4	15

Gesture type (intransitive, transitive, meaningless), prime location (left, right), prime type (congruent, incongruent) with their mean response times (ms), accuracy (%), and their standard errors of the means, for Experiment 2 with words as primes are listed.

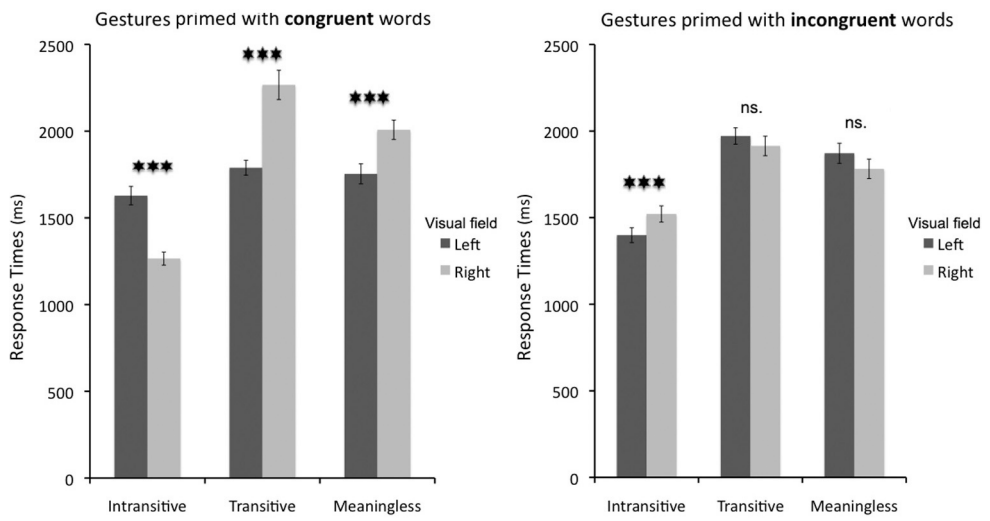


FIGURE 5 | Response times to correctly categorized intransitive gestures, tool use pantomimes, and meaningless hand movements primed by congruent or incongruent linguistic cues presented in the right or left visual field. Intransitive gestures were greatly facilitated by congruent linguistic cues on the right, whereas transitive gestures and meaningless movements showed the opposite effect. Incongruent linguistic cues affected the categorization of only intransitive gestures. Asterisks indicate differences with Bonferroni-corrected *p*-values of at least 0.001 (***).

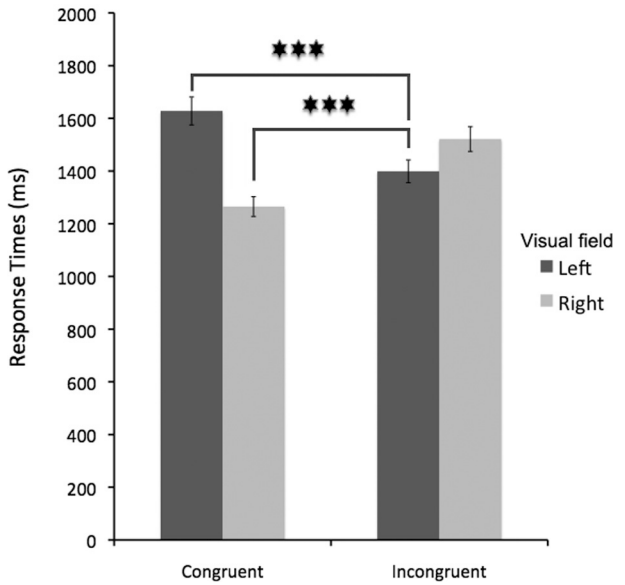


FIGURE 6 | The effects of incongruent left-sided cues on intransitive gesture categorization. There are two important comparisons that are considered. As can be predicted, such incongruent cues on the left significantly slowed the categorization of intransitive gestures as compared to congruent cues on the right. Yet, at the same time their negative impact was weaker than that of congruent cues presented on the left. This effect is consistent with an idea that right-hemisphere processing is also important in the categorization of conventionalized intransitive gestures. Asterisks indicate differences with Bonferroni-corrected *p*-values of at least 0.001 (***).

been described in the previous paragraph, with an emphasis on the effect that incongruent cues on the right slowed participants' responses.)

Discussion of Experiment 2

Because for categorization accuracy none of the differences between intransitive and transitive gestures was significant, in the discussion we will again focus only on response time results. It should be noted, though, that comparable accuracy in the two conditions indicates that both of the meaningful gesture categories have fine-grained representations in the brain, and the retrieval of these representations cannot be easily interfered with. In healthy participants, the differences in access and/or interference effects are only or primarily apparent when response times are analyzed, although in patients differences in accuracy following left- or right-sided lesions are often quite clear (Roy et al., 1991; Foundas et al., 1999; Haaland et al., 2000; cf. Rapcsak et al., 1993; Dumont et al., 1999; Mozaz et al., 2002, see also Stamenova et al., 2010).

Similarly to Experiment 1, intransitive ("conversational") gestures were again categorized significantly faster than transitive (tool use) pantomimes and meaningless hand movements. Yet, this time the categorization efficacy also differed between the latter two, with correct responses to transitive gestures being significantly slower than to meaningless actions. As noted above, the better performance with intransitive gestures is quite consistent with an earlier report on differences in accuracy observed during imitation of the two gesture categories under time constraints (Carmo and Rumiati, 2009). Indeed, these and our current results, as well as the outcomes of other behavioral (e.g., Mozaz et al., 2009) and recent neuroimaging studies on intransitive and transitive gestures support a view that transitive actions, as belonging to a less familiar category, rather than being differently represented—i.e., more left lateralized—are more difficult to process and/or perform [Kroliczak and Frey, 2009; Króliczak, 2013b; but cf. behavioral and neuroimaging results of Villarreal et al. (2008); see also Stamenova et al., 2010]. Interestingly, in the context of Experiment 2, this can be also said when their categorization is compared with that of actions deprived of meaning. Namely, meaningless actions were also categorized with greater ease than transitive gestures. Although meaningless actions were also categorized with lowest accuracy, speed-accuracy trade-off cannot be the major factor involved and its effect must have been combined with a greater adverse impact of linguistic cues on the categorization of transitive gestures.

As to the impact of these laterally presented cues in the form of words or short phrases on categorization, all the three gesture types were affected by congruent primes presented on the right. Yet it was only the categorization of intransitive gestures which—counter to a hypothesis of their more bilateral representations—was greatly facilitated, whereas the processing of transitive and meaningless actions was substantially hindered (as compared to the left-sided cues of the same kind). Conversely, the impact of incongruent linguistic cues was observed only for the intransitive gesture category, and it was actually the opposite of what was found for congruent primes. Namely, whereas right-sided congruent linguistic cues have facilitated performance, incongruent primes presented on the right have now slowed down the categorization of intransitive gestures.

Even though the latter finding is consistent with a view that the representations of intransitive gestures—similarly to language skills, with which they must be closely related (Kroliczak et al., 2011)—are strongly left lateralized, this interpretation should be exercised with caution. After all, although the verification of an incongruent linguistic cue from the left visual field, i.e., processed first in the right hemisphere, takes significantly longer than the evaluation of a congruent cue in the left hemisphere, nevertheless, and quite surprisingly such verification takes significantly less time than the processing of a congruent cue in the right hemisphere. This is not what would be expected if the representations of intransitive gestures were exclusively left lateralized.

The above-mentioned counterintuitive sensitivity to right hemisphere processing further suggests that intransitive gestures are represented somewhat differently from transitive pantomimes. The latter, conversely to intransitive but similarly to meaningless movements, were adversely affected by congruent linguistic cues presented on the right (i.e., projected to the left hemisphere). This could be due to the fact that some of its processing is either incompatible with, or perhaps engages excessively, the mechanisms to be also involved in their categorization. A different kind of representation for tool use gestures is also suggested by the lack of sensitivity to irrelevant linguistic cues (cf. Kroliczak et al., 2006), irrespective of the presentation side.

GENERAL COMMENTS

Consistently with earlier reports (Carmo and Rumiati, 2009; Kroliczak and Frey, 2009; Króliczak, 2013b), this study provides further evidence supporting an idea that intransitive gestures as less complex, highly conventionalized, and for that reason more often seen and used in naturalistic settings, are also easier to categorize as compared to rarely perceived and performed transitive gestures (tool use pantomimes), as well as meaningless hand movements. This is the case regardless of the testing conditions. Moreover, in the context of additional pictorial cues (i.e., images of hand postures for intransitive, and tools for transitive gestures), the response facilitation observed for both gesture categories was in the same direction, thus implying the involvement of some common mechanisms. Even though transitive gestures, perhaps as more difficult to retrieve in the first place, gained way more from these "prompts," as such, our results from a study using pictures as primes do not undermine a view that the two gesture categories might be processed within a common network. After all, the finding that the categorization of both gesture types (though much less in the case of intransitive gestures) was more efficient when the relevant pictorial cues were presented on the right—i.e., projected to the left hemisphere—is yet another piece of evidence that the understanding and control of meaningful gesture depends to a high degree on left-lateralized representations of praxis skills. It should be emphasized still again, though, that intransitive gestures depend substantially less on their input. (Yet, they are easier anyways.)

Consistent with the observation that intransitive gestures may be somewhat less lateralized—or rather more bilaterally represented—is our second major finding, namely that of their particular sensitivity to linguistic cues processed in both hemispheres. On the one hand, a dramatic facilitation in categorizing them as "conversational" following right-sided words or phrases supports the view of their dependence on left-lateralized mechanisms, which might be common with language functions (cf. Kroliczak et al., 2011; Vingerhoets et al., 2013; see also Goldenberg, 2013b; Króliczak, 2013a). On the other hand, although not surprisingly their categorization is substantially slower when relevant cues are first processed in the right hemisphere, this processing is in fact more detrimental than a verification that a right-sided cue is irrelevant. These findings are in fact consistent with a very long-standing conviction (e.g., Morlass, 1928) that the ability to perform and understand conventionalized (intransitive) gestures, while relying on general praxis representations, may also call for mechanisms and skills (e.g., social knowledge) implemented in different brain areas, including the right hemisphere. As suggested in the Introduction, this idea has indeed prominently figured in modern theories of praxis (cf. Gonzalez Rothi et al., 1991) implying that the mechanisms involved in retrieval of intransitive actions (including manual emblems) may be distributed across both hemispheres.

Finally, and quite unexpectedly, transitive gestures do not show much affinity to relevant linguistic cues, since their categorization was much slower in their presence and resembled that of meaningless actions. Yet, one cannot judge from such data that their representations are not left lateralized.

LIMITATIONS OF THE STUDY

It would be best if eye movements were monitored in such a paradigm, although prime duration of only 150 ms and the immediate mask make it less of a problem. It would be also better if primes appeared simultaneously in the right and left visual field, and attention to these lateralized primes was directly controlled for by an additional central cue. (For any further suggestions on and/or criticisms of visual half-field paradigms, see Hunter and Brysbaert, 2008).

CONCLUSIONS

In sum, this study shows evidence that the categorization of intransitive gestures may also draw on contributions from processes or mechanisms taking place outside of the left-lateralized praxis representation network. Indeed, it is justified to say that some of these processes (or mechanisms) might be located in the right cerebral hemisphere. Furthermore, and quite surprisingly, this seems to be particularly true when linguistic processing is involved. Yet, this conclusion would be much stronger were it not for the fact that such linguistic cues also affect the processing of tool use gestures in a rather unexpected way.

APPENDIX: MEANINGFUL STIMULUS VIDEOS

Intransitive gestures: Beckoning, Counting, Flicking, Hitchhiking, Pointing, Scolding, Shooing, Snapping, Stopping, Talking, Wavering, Waving.

Transitive gestures: Dialing, Painting, Pounding, Pouring, Reeling, Scrubbing, Sewing, Typing, Unlocking, Using a remote control, Using a spoon, Writing.

AUTHOR CONTRIBUTIONS

This project was conceptualized by Honorata Helon and Gregory Króliczak. Data was collected by Honorata Helon, and analyzed by Gregory Króliczak and Honorata Helon. The manuscript was written by Gregory Króliczak and Honorata Helon.

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Switching between global and local levels: the level repetition effect and its hemispheric asymmetry

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The global level of hierarchical stimuli (Navon's stimuli) is typically processed quicker and better than the local level; further differential hemispheric dominance is described for local (left hemisphere, LH) and global (right hemisphere, RH) processing. However, neuroimaging and behavioral data indicate that stimulus category (letter or object) could modulate the hemispheric asymmetry for the local level processing. Besides, when the targets are unpredictably displayed at the global or local level, the participant has to switch between levels, and the magnitude of the switch cost increases with the number of repeated-level trials preceding the switch. The hemispheric asymmetries associated with level switching is an unresolved issue. LH areas may be involved in carrying over the target level information in case of level repetition. These areas may also largely participate in the processing of level-changed trials. Here we hypothesized that RH areas underly the inhibitory mechanism performed on the irrelevant level, as one of the components of the level switching process. In an experiment using a within-subject design, hierarchical stimuli were briefly presented either to the right or to the left visual field. 32 adults were instructed to identify the target at the global or local level. We assessed a possible RH dominance for the non-target level inhibition by varying the attentional demands through the manipulation of level repetitions (two or gour repeated-level trials before the switch). The behavioral data confirmed a LH specialization only for the local level processing of letter-based stimuli, and detrimental effect of increased level repetitions before a switch. Further, data provides evidence for a RH advantage in inhibiting the non-target level. Taken together, the data supports the notion of the existence of multiple mechanisms underlying level-switch effects.

Keywords: hemispheric asymetry, hierarchical stimuli, switching, level repetition, inhibition

INTRODUCTION

Visual processing of global and local features of objects has been widely investigated with hierarchically organized stimuli (Navon, 1977), which are large (global) letters made up of mutually identical small (local) letters. These stimuli are thought to provide an experimental simplification of the complex multilevel natural visual environment (List et al., 2013). A functional hemispheric asymmetry is classically reflected by a right hemisphere (RH) advantage for global processing and a left hemisphere (LH) advantage for local processing. This notion is supported by extensive evidence from brain damaged patients (Robertson et al., 1988; Lamb et al., 1990; Robertson and Lamb, 1991), brain imagery investigations (Fink et al., 1996; Martinez et al., 1997; Han et al., 2000), event-related potentials (ERP) studies (Grabowska and Nowicka, 1996; Proverbio et al., 1998; Evans et al., 2000) and behavioral experiments involving lateralised presentation of compound stimuli (Blanca et al., 1994; Hübner, 1997; Evert and Kmen, 2003; Hübner et al., 2007). according to ERP data, the hierarchical processing modulates activities in the visual cortex at latencies as short as 110 ms (Han et al., 2000). In the early visual (prestriate) processing areas, attention to the global or local levels is respectively associated with activations in the right lingual gyrus and the left inferior occipital cortex (Fink et al., 1996). This asymmetry is also observed in higher level processing areas, which may mediate the voluntary distribution of selective attention across the complexity levels (Rafal and Robertson, 1995) and modulate computations performed in the prestriate cortex (Fink et al., 1996). This is consistent with evidence of impaired global processing in patients with right temporal-parietal lesions, but impaired local processing with left temporal-parietal lesions (Robertson et al., 1988; Robertson and Lamb, 1991).

An alternative approach is that the hemispheric asymmetry for local level processing is modulated by the stimulus category as the classical hemispheric asymmetry for global/local processing is not observed when the hierarchical stimuli are not made of alphabetic material, (Bedson and Turnbull, 2002). According to both positron emission tomography (PET) data (Fink et al., 1996, 1997b) and to behavioral findings from experiments with visual half-field presentation (Keita and Bedoin, 2011), RH dominance can be observed for the local processing of object-based hierarchical stimuli when the stimulus category (letter vs. object) is known in advance. According to the lateralisation of cerebral networks

specialized for the stimulus category, the highly demanding local level processing is assumed to engage one hemisphere more than the other.

In contrast to the demands of selective attention paradigms in which attention is focused at one level of complexity, targets in divided attention paradigms are equiprobably but unpredictably displayed either at the global or local level. Decreased performance is then observed for changed-level as compared to repeated-level trials (Ward, 1982; Robertson, 1996; Lamb et al., 1999), an effect which has been dissociated from response- and stimulus-changing effects (Robertson, 1996; Filoteo et al., 2001; List et al., 2013). This difference may be due to attentional processes, as the advantage for repeated-level trials may reflect a level-specific priming effect and the carry-over of target level information from the last trial may involve the left inferior parietal lobe. Conversely, decreased performance for changed-level trials may relate to additional attention switching performed between the two processing modes. The switch-cost is independent of the resolution or the actual size of the targets (Fink et al., 1996; Kim et al., 1999; Filoteo et al., 2001) and is not strictly based on a change in the selection of spatial frequencies (Lamb and Yund, 1996a). Therefore, switching between levels within a hierarchical stimulus is not strictly based on a zoom lens of attention, but also on changes in the attentional weights associated with each level (Robertson, 1996).

When considered as a unitary mechanism, switching between levels is often described as an executive attentional mechanism mainly based on LH areas. Its neural bases have been assessed by increasing the overall demands imposed on this process. These demands are increased when a switch trial is separated from the last switch by a small length of time (Wilkinson et al., 2001), and when a high number of level-changed trials occur in an experiment (Fink et al., 1997a), which is associated with activations in the precuneus, the left supplementary motor area, and the left medial parietal areas. This is consistent with ERP evidence that a positive potential peaking at 290 ms over the left parietal and left posterior temporal regions was higher for changed-level trials than for repeated-level trials (Schatz and Erlandson, 2003). However, the neuropsychological evidence is mixed. An impairment of global/local level-switches have been described in cases of both left dorsal parietal lesions (Rafal and Robertson, 1995) and right temporal-parietal lobe damage (Filoteo et al., 2001). This suggests the involvement of this right cortical area in monitoring attentional weights to different hierarchical levels for switch trials.

Varying the number of repeated-level trials before a changed-level trial may specifically modulate the demands for the inhibition of the inappropriate level of analysis. For example, the magnitude of the switch cost has been shown to increase with more targets identified at the same level before the switch (Wilkinson et al., 2001). Compared with a level switch performed after two repeated-level trials, a switch performed after four or six repeated-level trials is associated with bilateral activation of a parietal-motor area, which suggests that right lateralised are crucial for inhibiting the inappropriate level of analysis.

The current study was aimed to replicate the modulation of hemispheric asymmetry for the local level processing of hierarchical stimuli by the stimulus category. Therefore, better performance was expected for local targets presented in the right visual field (RVF-LH) than in the left visual field (LVF-RH) only for letter-based hierarchical stimuli. As this effect has been observed only in between-subject comparisons, we sought to replicate it with a within-subject design in a divided attention task. The experiment was also designed to test the prominent involvement of right cerebral areas in inhibiting the inappropriate processing level when performing an intra-stimulus (hierarchical) switch between levels. Changed-level trials were presented after either two or four repeated-level trials to modulate the demands on this inhibitory process. We expected switching after four repeated-level trials to require inhibitory processing and therefore to be better performed in the LVF-RH than in the RVF-LH. We assess the detrimental effect of response changing by comparing a no-change condition (the visual field, the target level, and the response were the same as in the preceding trial) with a changed-response condition (the only difference with the previous trial was the target (i.e., the response). In contrast to the cost of switching, the cost of response changing was not expected to be lower for the targets displayed to the LVF-RH, which therebyhighlights the specificity of inhibiting the irrelevant complexity level as one of the mechanisms underlying the between-level switching process.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-two university students (22 female and 12 male; mean age = 22.8 years, $\pm$3.3) performed both the letter block and the object block tasks. All the participants had normal or corrected-to-normal vision and were strongly right-handed (9 or 10 right-handed responses out of a total of 10 of the most reliable items of the Edinburgh Handedness Inventory). They gave informed and written consent to participate.

STIMULI

The stimuli included a block of hierarchical letters (letter block) and a block of hierarchical objects (object block) drawn in black on a white background. Their order of presentation was counterbalanced across participants. The hierarchical letters were each a large (global) letter made up of smaller (local) letters (**Figure 1**). Global and local letters always differed within a hierarchical stimulus. One of the two targets (E or M) was located either at the local or the global level, while the distractor letters (H, T, or A) were presented at the other level. The 96 experimental trials were equally displayed either to the RVF-LH or to the LVF-RH. In each hemifield, the target appeared at the local level in half of the trials and at the global level in the other half. The presentations of E and M were equally likely both in each of the four level by field combinations and in being associated with each of the three distractor letters. In the letter block, we used 120 filler trials, which each involved one of the target letters. The side of presentation and the target level of the filler trials were equated following the same rules as for the experimental trials. The global letter subtended 3.8°(horizontal) $\times$ 4.0°(vertical) of visual angle; the local letter subtended 0.35° (horizontal) $\times$ 0.4° (vertical) of visual angle and were separated by 0.1°.

The object block also included 96 experimental trials and 120 filler trials. The objects presented at the global and the local levels

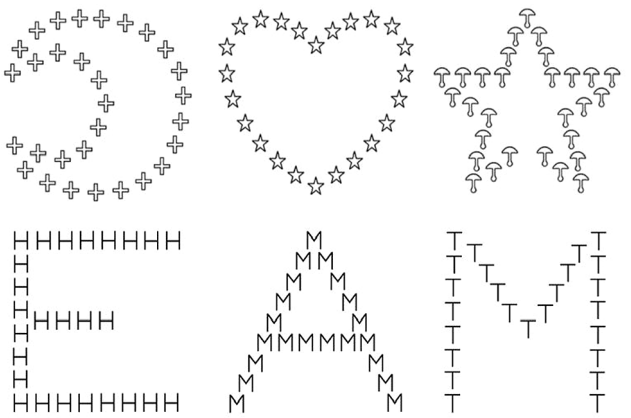


FIGURE 1 | Examples of figures used as object-based hierarchical stimuli with the star and the moon as the targets, and letter-based hierarchical stimuli with E and M as the target letters.

always differed within a hierarchical stimulus. One of the two targets (star or moon) was displayed either at the local or global level, while a distractor object (mushroom, cross, or heart) was presented at the other level (**Figure 1**). The drawings were as simple as possible, but the shape of the objects was slightly more complex than those of the letters as they were made up of 24 to 32 elements, while the letters were made up of 16 to 26 elements. The size of the local and global objects was the same as the size of the local and global letters, with the same spacing between the elements. The same rules as in the letter block were applied regarding the presentation of the 96 experimental trials and the 120 filler trials for the level, the visual field, and the combination of targets with the distractor objects.

GENERAL PROCEDURE

Each participant was tested individually in a sound attenuated booth and sat in front of an Apple Macintosh iBook at a constant distance of 57 cm from the screen. At the beginning of each trial, a fixation point (=) appeared at the center of the screen for 1500 ms. The hierarchical stimulus was displayed during the last 175 ms of the display of the fixation point, either to the RVF or the LVF. Its nearest border was 2° distant from the fixation point. The filler trials were distributed through the list to avoid any regularity within the presentation sequence. The sequence consisted of 1–3 consecutive left or right displays, 1–5 consecutive identical targets, and 1–4 repeated-level trials to prevent participants from learning any rules regarding the following stimulus.

The 192 letter- and object-based experimental trials were equally distributed among four conditions. The changed-level trials appeared either after two (48 trials) or four (48 trials) repeated-level trials. The stimuli presented in the no-change condition (48 trials) were preceded by two repeated-level trials. To avoid confounding the level-switch cost and the costs due to response changing or to spatial shifting, the experimental trials in both changed-level conditions and in the no-change condition always followed a trial displayed to the same hemifield and containing the same target. In the no-change condition, the target in $n-1$ and $n-2$ were located at the same level as the n target. To assess the cost associated with reponse changing, performance in the no-change condition was compared with performance in the changed-response condition (48 trials). In the changed-response condition, the n trial was preceded by two repeated-level trials and $n-1$ was displayed in the same hemifield but it contained a different target (see **Figure 2** for examples of the four context conditions).

The task was to decide whether the hierarchical stimulus contained E or M (in the letter block) and the moon or the star (in the object block). The participants were asked to respond as quickly and accurately as possible by pressing one of the two associated keys with the left or right index finger. In each hemifield, the same proportion of trials required left and right index responses, in order to maintain the same probability of a stimulus-response compatibility (Simon effect) to occur in each experimental condition. The next trial began 1500 ms after the response. Response times (RT) and accuracy were recorded for each trial. A rest period was proposed between the two blocks, and each of them began with 12 practice trials. Each block was punctuated with a break.

DATA ANALYSIS

Mean RTs for correct responses and errors rate (ERs) were analyzed using four-factor repeated-measure ANOVAs with a Greenhouse-Geisser correction, with four within-subject factors: category (letter, object), level (global, local), visual field (RVF-LH, LVF-LH), and context (no-change, changed-response, switch after two level repetitions, switch after 4 level repetitions). Contrasts were reported regarding the expected differences between conditions. The alpha level was set at 0.05. The effect size was estimated by calculating partial eta-squares (η_p^2) and, in accordance with Cohen (1988), it was considered as small if $\eta_p^2 = 0.01$, medium if $\eta_p^2 = 0.06$, and large if $\eta_p^2 = 0.14$.

RESULTS

The analysis revealed a main effect of category with shorter RTs, $F(1,31) = 20.96$, $p < 0.0001$, $\eta_p^2 = 0.40$, and better response accuracy, $F(1,31) = 23.53$, $p < 0.0001$, $\eta_p^2 = 0.43$, for letter-based than for object-based stimuli. A main effect of level was also observed, as indexed by shorter latencies, $F(1,31) = 13.16$, $p < 0.001$, $\eta_p^2 = 0.30$, and fewer errors, $F(1,31) = 7.72$, $p < 0.01$, $\eta_p^2 = 0.20$, for the global than for the local level. The level × field × category interaction was obtained on RTs, $F(1,31) = 4.43$, $p < 0.044$, $\eta_p^2 = 0.013$, and constrasts indicated the expected difference in hemispheric asymmetry for the local level according to the stimulus category. As illustrated in **Figure 3**, the identification of local target letters was faster in the RVF-LH than in the LVF-RH, $F(1,31) = 11.86$, $p < 0.002$, $\eta_p^2 = 0.03$, whereas this index of LH dominance for local processing disappeared for object-based stimuli, $F(1,31) < 1$.

The visual field effects (VFE = LVF − RVF) are presented in **Table 1**. As for local targets, the VFE was significantly lower for object-based than for letter-based stimuli, $F(1,31) = 5.29$, $p = 0.0283$, $\eta_p^2 = 0.15$.

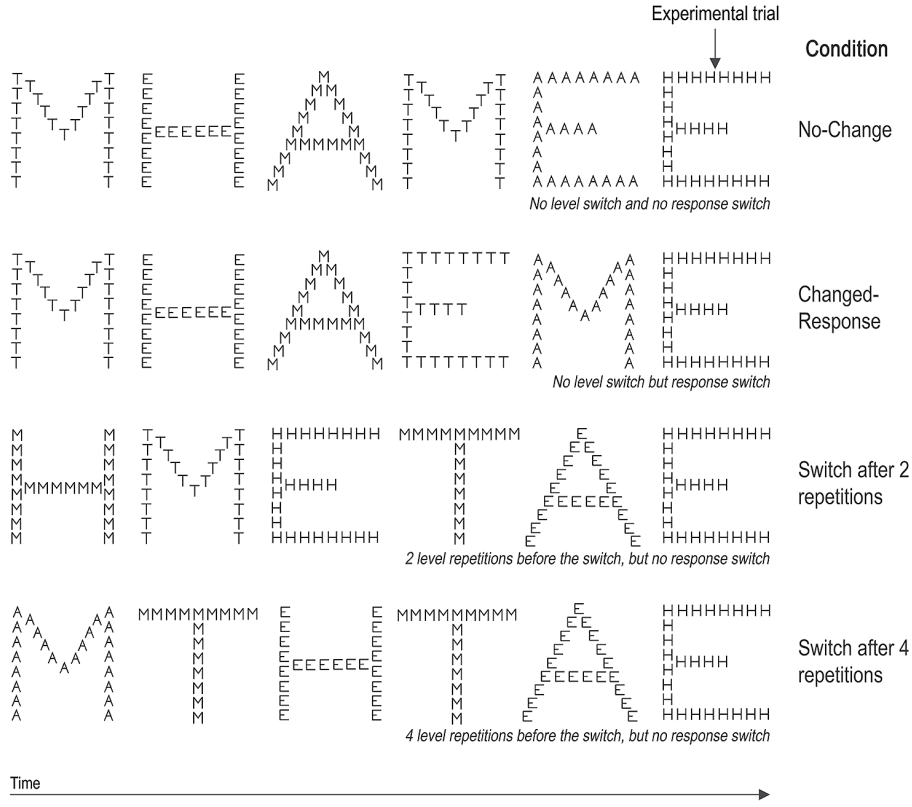


FIGURE 2 | Examples of context stimuli sequences regarding each of the context conditions.

The level × field × category interaction did not reach significance with ERs, $F(1,31) = 2.16$, $p = 0.15$. However, any phenomenon of speed-accuracy trade-off can be excluded according to the pattern of results observed in **Figure 4**. A RVF-LH advantage was indeed recorded for the local letters, $F(1,31) = 6.24$, $p < 0.019$, $\eta_p^2 = 0.06$, while no hemispheric asymmetry occurred for response accuracy regarding the local processing of hierarchical objects, $F(1,31) < 1$. The VFE was significantly higher on error rates for local letters than for local objects, $F(1,31) = 4.76$, $p = 0.0368$, $\eta_p^2 = 0.13$.

We obtained a main effect of context with RTs, $F(3,93) = 33.57$, $p < 0.0001$, $\eta_p^2 = 0.52$, which could not be explained by the cost due to switching between responses, since the comparison between the no-change and the changed-response conditions was not significant, $F(1,93) < 1$ (**Figure 5**). However, as predicted, the main effect of context reflected the dramatic increase in response latency with the necessity to switch between levels, as confirmed by the difference between no-change and switch after two repetitions conditions, $F(1,93) = 19.40$, $p < 0.0001$, $\eta_p{}^2 = 0.17$. Additionally, RTs for changed-level trials were significantly longer after four rather than two repeated-level trials, $F(1,93) = 20.63$, $p < 0.0001$, $\eta_p^2 = 0.18$. The analysis of ERs confirmed the main context effect, $F(3,93) = 13.87$, $p < 0.0001$, $\eta_p{}^2 = 0.31$, and the lack of significant cost due to switching between responses, $F(1,93) < 1$ (**Figure 6**). Consistent with the pattern of results on RTs, the level-switch cost was observed with ERs, $F(1,93) = 11.61$, $p < 0.001$, $\eta_p^2 = 0.11$, as was the detrimental effect of increased number of level repetitions before a level switch, $F(1,93) = 4.35$, $p < 0.04$, $\eta_p^2 = 0.04$.

Regarding hemispheric asymmetry, a context × field interaction was observed with RTs, $F(3,93) = 2.91$, $p < 0.039$, $\eta_p^2 = 0.09$, indicating two phenomena (**Figure 5**). One, the RVF-LH advantage was much higher when a switch occurred after two level repetitions, $F(1,93) = 7.60$, $p < 0.007$, $\eta_p^2 = 0.08$, than in the no-change condition, $F(1,93) = 4.23$, $p < 0.043$, $\eta_p^2 = 0.04$. Two, the detrimental effect of the increased number of level repetitions before switching was significant for targets displayed to the RVF-LH, $F(1,93) = 32.69$, $p < 0.0001$, $\eta_p^2 = 0.26$, but not for targets displayed to the LVF-RH, $F(1,93) = 3.25$, $p = 0.08$. Similarly, the VFE significantly differed between switching after two or after four level repetitions, $F(1,93) = 7.66$, $p = 0.0068$, $\eta_p^2 = 0.08$ (**Table 2**).

The analysis with ERs confirmed this pattern of results, but the context × field interaction did not reach significance, $F(3,93) = 1.40$, $p = 0.24$ (**Figure 6**). However, response accuracy in the changed-level conditions was significantly affected by the visual field in the expected direction.

The contrasts provided convergent evidence for a RH advantage in inhibiting the non-target level. One, switches required in the most difficult condition regarding the inhibitory process (switch

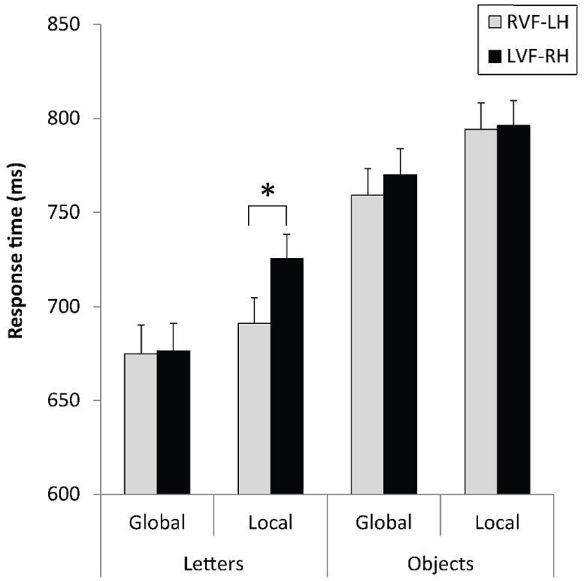


FIGURE 3 | Mean response times and standard errors for letter-based and object-based hierarchical stimuli displayed to the right (RVF-LH) or left visual field (LVF-RH), as a function of the level of the target (global, local). *$p < 0.05$.

after four repetitions) strongly tended to be more accurately performed for targets displayed to the LVF-RH than to the RVF-LH, $F(1,93) = 3.56$, $p = 0.06$, $\eta_p^2 = 0.04$. Similarly, the VFE stringly tended to differ after four and after two repeated levels, $F(1,93) = 3.83$, $p = 0.0608$, $\eta_p^2 = 0.04$. Two, parallel to the RT data, switches were negatively affected by the increased number of previous repeated-level repetitions in the RVF-LH, $F(1,93) = 10.69$, $p < 0.002$, $\eta_p^2 = 0.10$, but not in the LVF-RH, $F(1,93) < 1$.

DISCUSSION

The goals of the study were to assess the modulation of hemispheric asymmetry for local processing of visual hierarchical information by the stimulus category and to selectively address inhibition of the inappropriate level of analysis as one of the specific components of the ability to switch between levels. We aimed to stress the implication of the RH in the inhibition process in switching after more repetitions of the target at the same level. Taken together, the results replicated the typical LH advantage for the identification of local targets in letter-based hierarchical stimuli. The second main finding of our study was that the increased number of level repetitions before a level switch was detrimental to the speed and the accuracy of the hierarchical stimulus processing in the RVF-LH, but not in the LVF-RH, suggesting that right-sided cerebral areas are much efficient in the inhibition mechanism involved in switching between levels.

THE INFLUENCE OF STIMULUS CATEGORY ON HEMISPHERIC ASYMMETRY IN LOCAL PROCESSING

Many findings support the notion that the RH is more efficient in the global processing of compound stimuli, while the LH is biased toward attending to and processing its local elements. However, this has not been found in a number of studies with rapid lateralised presentations (Van Kleeck, 1989; Yovel et al., 2001). The results obtained in our experiment confirmed that the local processing of object-based hierarchical stimuli is not associated with the typical LH advantage. Therefore, the functional hemispheric asymmetry in perceptual processes may be modulated by higher order attentional "top-down" mechanisms due to characteristics of the task. These mechanisms probably rely on temporal-parietal areas and play a supervisory role in the attentional control for global/local processing within the prestriate cortex (Yamaguchi et al., 2000). For example, the classical hemispheric asymmetries for global/local processing are more robust in divided- than focused-attention tasks (Van Kleeck, 1989; Heinze et al., 1998; Yovel et al., 2001), and when solving information conflict between levels is necessary (Hübner and Malinowski, 2002; Malinowski et al., 2002; Volberg and Hubner, 2004, 2006; Hübner and Volberg, 2005; Hübner et al., 2007). Additionally, hemispheric asymmetries due to the global-local distinction can be obscured by some aspects of the material which may produce co-varying effects due to the involvement of other processes which are also lateralised.

The present findings support the notion that the category of information is one of the co-varying factors associated with hemispheric asymmetries in processing hierarchical stimuli, since LH dominance was obtained for local letters but not for local

Table 1 | Mean response times in milliseconds and errors rates (standard errors in parenthesis) across visual field conditions.

		Letter-based stimuli		Object-based stimuli	
Target level		**Global**	**Local**	**Global**	**Local**
RVF-LH	TR	675 (15.49)	691 (13.96)	759 (14.34)	794 (14.16)
	ER (%)	2.47 (0.53)	3.52 (0.68)	6.77 (0.93)	6.77 (1.04)
LVF-RH	TR	676 (14.82)	725 (12.99)	770 (14.10)	796 (13.47)
	ER (%)	1.17 (0.42)	5.73 (0.88)	5.34 (0.87)	6.25 (0.96)
Difference:LVF-RVF	TR	1	34	11	2
	ER (%)	−1.3	2.21	−1.43	−0.52

RVF-LH, right visual field-left hemisphere; LVF-RH, left visual field-right hemisphere.

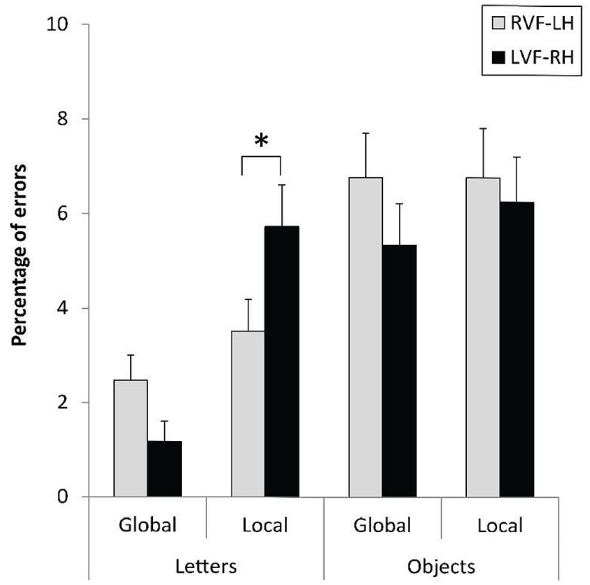


FIGURE 4 | Mean error rates and standard errors for letter-based and object-based hierarchical stimuli displayed to the right (RVF-LH) or left visual field (LVF-RH), as a function of the level of the target (global, local). $^*p < 0.05$.

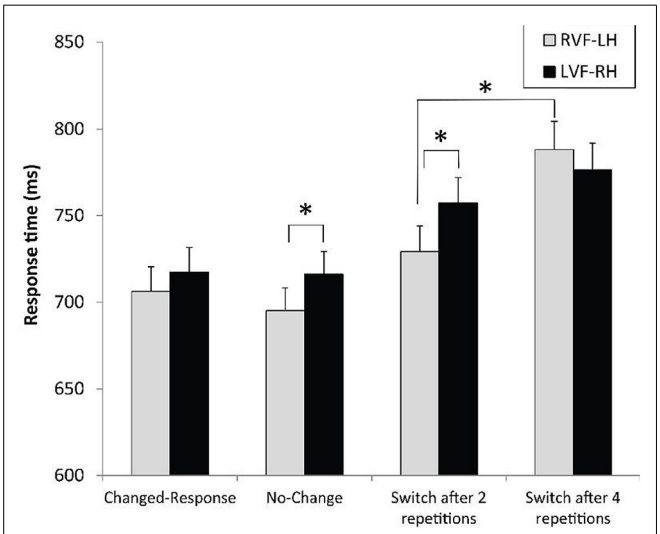


FIGURE 5 | Mean response times and standard errors for letter-based and object-based hierarchical stimuli according to the context preceding the experimental trial and the visual field of presentation. $^*p < 0.05$.

objects. We attemptedto modulate hemispheric asymmetry specially regarding the local level, which may impose greater perceptual demand on target identification (Fink et al., 1997b). To compensate for this difficulty, the local level of compound stimuli may engage additional mechanisms to improve the processing of small elements. Therefore, lateralised cognitive mechanisms may be engaged in the local processing either because they underly the processing of details or because they are specialized in the category of the stimulus content. This may result in the selective engagement of left- or right-sided areas in local target identification for hierarchical letters and hierarchical objects, respectively. This notion is supported by Bedson and Turnbull (2002) who also reported LH dominance in the case of local processing when the targets were letters only but not when they were shapeswhich had fewer less "linguistic" properties. The data here are consistent with this pattern of findings for both rapidity and accuracy of responses by using compound letters and compound object drawings.

Consistent with evidence of higher involvement of the RH areas for local processing of object-based hierarchical stimuli found with PET data (Fink et al., 1996, 1997a), we have previously found dominance of RH areas for local objects and LH for local letters with the same material and task as used in the current study but with a between-subject design (Keita and Bedoin, 2011). In the present experiment, the LH dominance for local processing disappeared in case of object-based hierarchical stimuli, but no RH dominance was actually observed. This lack of clues for RH dominance may be partly due to the within-subject design. Indeed, in a between-subject design, the participants respond to only one category of information (alphabetic vs. non-alphabetic) which may lead to assigning a value to the stimulus content, resulting in important modulation of hemispheric asymmetry by the category. In contrast, in the within-subject design used in the present experiment, the participants performed the task on letter-based and object-based hierarchical stimuli, which may reduce the importance devoted to the stimulus category.

The present findings also differed from those in our previous study in which a significant advantage for global targets was not observed, despite the global/local size ratio was the same in both studies. This global/local size ratio was chosen to get the same perceptual salience for local and global targets (Keita and Bedoin, 2011). The reason for the advantage for global targets in the current experiment is unclear, but the evidence suggests that attention was biased toward this level. The ability to select information against dominant information (here, the ability to select the local level) has been shown to rely on the left inferior parietal cortex (Mevorach et al., 2006), and the involvement of this LH area could contribute to mask the effect of the RH involvement in the local processing of object-based compound stimuli.

THE RIGHT HEMISPHERE INVOLVEMENT IN INHIBITION DURING SWITCHING

The difference in performance between the no-change trials and the changed-trials after two repetitions replicated the detrimental effect of switching on performance (Robertson, 1996). Previous evidence of its dissociations from response- and stimulus-changing effects (Robertson, 1996; Filoteo et al., 2001; List et al., 2013) is consistent with the findings here that switching between levels more dramatically decreased performance than changing motor responses between successive trials. Thus, this process appears to impose considerable demands on cognitive resources. The findings also indicate that a switch between levels which presents moderate difficulty (i.e., switch performed after two repetitions) is associated with LH dominance. The lack of

Table 2 | Mean response times in milliseconds and errors rates (standard errors in parenthesis) across context conditions.

Target level		Response-change	No-change	Switch after 2 repetitions	Switch after 4 repetitions
RVF-LH	TR	706 (14.37)	695 (13.44)	729 (14.90)	788 (16.32)
	% of ER	3.00 (0.60)	2.47 (0.56)	5.34 (0.85)	8.73 (1.11)
LVF-RH	TR	718 (13.89)	716 (12.77)	758 (14.59)	776 (15.65)
	% of ER	2.74 (0.66)	2.74 (0.63)	6.25 (0.92)	6.77 (0.97)
Difference:LVF-RVF	TR	12	21	29	−12
	ER (%)	−0.26	0.27	0.91	−1.96

RVF-LH, right visual field-left hemisphere; LVF-RH, left visual field-right hemisphere.

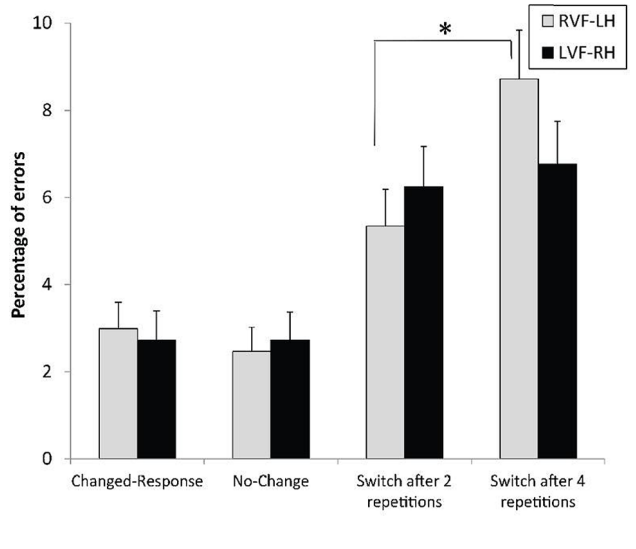


FIGURE 6 | Mean error rates and standard errors, according to the context preceding the experimental trial and the visual field of presentation. $*p < 0.05$.

significant LH dominance in the no-change condition emphasizes the specialization of some LH areas in switching attention between levels. This result is consistent with the notion that LH areas have high level of proficiency governing the switching between levels (Fink et al., 1997a; Wilkinson et al., 2001; Schatz and Erlandson, 2003).

As expected, many repetitions of targets at the same level prior to a switch between levels increased the switch cost. In this study, variation in the number of previous level repetitions was aimed at specifically modulating the demands imposed to inhibiting the inappropriate level of analysis. When these demands increased, some aspects of the findings reflected the crucial role of RH areas. The RH dominance for this inhibitory process was reflected by the restriction of the detrimental effect of numerous level repetitions before switching within the RVF-LH. As illustrated in **Figures 5** and **6**, the lack of effect of the number of previous repetitions before switching in the LVF-RH cannot be interpreted as the function of a ceiling effect. Consequently, the RH appears to present a high level of proficiency in performing inhibition upon the inappropriate processing level. Additionally, a trend toward better accuracy in the LVF-RH than in the RVF-LH for level switches performed after four level repetitions was observed. By increasing the task difficulty, this high demanding condition provided opportunities to record behavioral evidence of hemispheric asymmetry in selective attention mechanisms (Evert and Oscar-Berman, 2001). In this condition, the attentional load was probably sufficiently demanding to require the best distribution of hemispheric involvement for the inhibition operation to be performed. Thus, the data converge on the notion of the crucial role of RH areas in inhibiting the inappropriate processing level. Since LH dominance was, in contrast, observed for the overall switching process, these clues for RH dominance when the switch strongly relied on inhibition revealed a reverse pattern of hemispheric asymmetry. This difference also confirmed the notion that the inhibitory mechanism can be specifically addressed among the switching process, as disengagement is separately assessed in spatial attention shifting (Posner, 1988).

The RH dominance when inhibiting the irrelevant processing level is consistent with the crucial role of right-lateralised areas in various forms of inhibition. The underlying neural networks may be different, but disengagement in spatial attention shifting is achieved in a most competent manner by a right cortical area (i.e., the right posterior parietal area; Robertson and Rafal, 2000). Additionally, task-switching experiments (changes between processing rules or judgment criteria are required to process a series of trials) also implicate one kind of internally mediated attentional switching and researchers have consistently emphasized the role of right-lateralised areas in inhibiting the inappropriate task-set when switching from one task to another one (Aron et al., 2004; Rogers et al., 2006). Similarly, response inhibition and the control of impulsivity is known to involve prefrontal and frontal-parietal networks preferentially in the RH (Aron et al., 2003; Rubia et al., 2003; Verbruggen et al., 2010). In the light of the consistent evidence for the major role of RH areas in various forms of inhibition, one potential interpretation of our pattern of results is that of evidence for the crucial role of RH areas in inhibiting information located at the inappropriate level or inhibiting the cognitive mechanisms involved in the inappropriate level of analysis of complex visual scenes. According to the *mechanism activation* hypothesis (Lamb and Yund, 1996b), each level of complexity is associated with specific neural mechanisms whose computations are not necessarily based on spatial frequency nor determined directly by the size of the attentional window, but are specific to the position

of information within a hierarchical structure defined in terms of spatial hierarchical relations. Therefore, the level-repetition effect has been interpreted to occur at a relatively abstract stage of processing (Hübner, 2000). This may also be the case for the switch cost and the specific inhibitory mechanism assessed in our experiment.

The study has a few limitations that should be considered. One, although all the stimulus category and visual field effects pointed in the same expected directions when recorded on RTs and on ERs, the effects sometimes reached significance only for one of the outcome variables. Two, functional hemispheric asymmetries were investigated by using tachistoscopic lateralized presentation of visual stimuli, which has been shown to reliably reveal functional differences between the two hemispheres. However, a more precise localisation of the cerebral areas involved in the inhibitory process assessed in this study should be considered in future investigations, either by using brain imagery techniques or by observing the patterns of performance of patients with specific cerebral lesions. Nevertheless, the present data provide both new evidence regarding the role of both the hierarchical level of information and the stimulus category in elicitingthe involvement of right and LH areas in processing complex visual scenes and in switching between global and local levels of complex visual stimuli.

AUTHOR CONTRIBUTIONS

Luc Kéïta and Nathalie Bedoin designed experiments. Luc Kéïta, Nathalie Bedoin, Jacob A. Burack, and Franco Lepore wrote the main manuscript text. Luc Kéïta, Nathalie Bedoin, and Franco Lepore analyzed the data. Luc Kéïta and Nathalie Bedoin prepared figures. All authors (Luc Kéïta, Nathalie Bedoin, Jacob A. Burack, and Franco Lepore) reviewed the manuscript. Franco Lepore paid the manuscript fee.

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Brain reorganization as a function of walking experience in 12-month-old infants: implications for the development of manual laterality

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Hand preference in infancy is marked by many developmental shifts in hand use and arm coupling as infants reach for and manipulate objects. Research has linked these early shifts in hand use to the emergence of fundamental postural–locomotor milestones. Specifically, it was found that bimanual reaching declines when infants learn to sit; increases if infants begin to scoot in a sitting posture; declines when infants begin to crawl on hands and knees; and increases again when infants start walking upright. Why such pattern fluctuations during periods of postural–locomotor learning? One proposed hypothesis is that arm use practiced for the specific purpose of controlling posture and achieving locomotion transfers to reaching via brain functional reorganization. There has been scientific support for functional cortical reorganization and change in neural connectivity in response to motor practice in adults and animals, and as a function of crawling experience in human infants. In this research, we examined whether changes in neural connectivity also occurred as infants coupled their arms when learning to walk and whether such coupling mapped onto reaching laterality. Electroencephalogram (EEG) coherence data were collected from 43 12-month-old infants with varied levels of walking experience. EEG was recorded during quiet, attentive baseline. Walking proficiency was laboratory assessed and reaching responses were captured using small toys presented at mid-line while infants were sitting. Results revealed greater EEG coherence at homologous prefrontal/central scalp locations for the novice walkers compared to the prewalkers or more experienced walkers. In addition, reaching laterality was low in prewalkers and early walkers but high in experienced walkers. These results are consistent with the interpretation that arm coupling practiced during early walking transferred to reaching via brain functional reorganization, leading to the observed developmental changes in manual laterality.

Keywords: brain reorganization, human infants, reaching, walking, manual laterality, EEG coherence

INTRODUCTION

The development of hand preference in the first year of life has been described by many researchers as an unstable process marked by many shifts in hand use and arm coupling as infants learn to reach for and manipulate objects (Gesell and Ames, 1947; Goldfield and Michel, 1986; Corbetta and Thelen, 1996, 1999; Fagard and Pezé, 1997). Several studies have linked these developmental shifts in early goal-directed hand use to the emergence of fundamental postural and locomotor milestones. For example, Rochat (1992) documented a decline in bimanual reaching and an increase in one-handed reaching when infants learned to sit independently. Goldfield (1993), Corbetta and Thelen (2002), and Babik et al. (2014) further documented such decoupling in hand use in relation to the onset of hands-and-knees crawling. Finally, Corbetta and Bojczyk (2002), and more recently Berger et al. (2011) and Babik et al. (2014) observed a return to two-handed reaching toward the end of the first year when infants learned to stand and performed their first independent steps. This return to two-handed reaching was especially surprising given that the infants in those studies had been followed longitudinally since the age of 6–8 months. They had demonstrated the ability to reach for small objects with one hand for several months prior to walking onset, and as a result of such regular follow-up had become quite familiar with the task and at practicing one-handed reaching. This increase in bimanual reaching at the onset of upright locomotion was also found to be accompanied with a decline in preferred hand use (Corbetta and Thelen, 2002; Berger et al., 2011; although see Babik et al., 2014).

In most of these studies, the observed developmental fluctuations in bimanual reaching were not directly associated with the act of locomoting *per se* – fluctuations in arm use were documented when infants were sitting while reaching. Yet, the fact that changes in patterns of hand use in reaching occurred during specific periods of whole body postural reorganizations and gross motor skills learning suggested that some underlying developmental process might have linked changes in reaching with the

learning of the new fundamental motor skills being acquired. Following this reasoning, Corbetta and Bojczyk (2002) proposed a *transfer of learning* account (see also Corbetta and Thelen, 2002; Corbetta et al., 2006; Corbetta, 2009). In the context of self-produced locomotion, they argued that the novel and specific arm use activity associated with the processes of maintaining balance and coordinating arms and body movements to propel the body forward might have temporarily transferred to reaching until these gross motor skills were acquired, or became more routine-like. Specifically, the break in reaching coupling associated with the emergence of hands-and-knees crawling was seen as the product of actively learning to sequence and alternate the movements of the forearms in order to crawl. This act of newly practicing arm alternation during self-produced quadruped locomotion, in turn was assumed to have transferred to reaching, hence enticing the shift to a greater use of alternated, one-handed, non-lateralized reaching responses during that period of development (Corbetta and Thelen, 1999, 2002). Likewise, the return to bimanual reaching and continued decline in lateralized hand use observed toward the end of the first year was seen as the product of the extensive upper arm coupling that infants produce when actively controlling their upright balance with their arms in high guard position; i.e., with arms held up at or above shoulder level during stepping. Such arm coupling during early walking was considered to have transferred to reaching, hence again, entraining the rise in bimanual reaching responses documented during this critical learning period of upright balance control (Corbetta and Bojczyk, 2002; Corbetta and Thelen, 2002; Corbetta et al., 2006).

The pattern resemblance observed between the transient responses adopted in reaching and the specific arm use being practiced during specific postural–locomotor skill learning is consistent with the hypothesis that some transfer of learning may have occurred between locomotor and reaching skills; however, why and how such transfer would occur remains unclear. Corbetta and Bojczyk (2002) speculated that such transfers in behavioral patterning between locomotion and reaching might have occurred via functional brain reorganization. To support their arguments, these researchers referred to a number of classic studies in the neurosciences. These studies, performed with adults and animals, have demonstrated the effects of specific motor practice and novel sensory-motor experiences on brain plasticity and cortical functional reorganization, particularly in the sensory-motor cortex (Jenkins et al., 1990; Merzenich and Jenkins, 1993; Karni et al., 1998; Kleim et al., 1998; Petersen et al., 1998, to cite a few). Of particular interest is the fact that these studies found cortical reorganization to be closely related to the task that was being learned and practiced, and hence, to the specific limbs, body parts, and sensory organs that were used to achieve the task. Some studies even found a direct mapping between brain hemispheric organization and upper arm coupling. For example, Andres et al. (1999) have shown that the acquisition of bimanual skills increased coupling of homologous cortical sensory-motor areas. And bilateral versus unilateral limb training in a reaching task was found to differentially affect dendritic branching of neurons in the rat motor-sensory forelimb cortex (Greenough et al., 1985). Likewise, the use of one arm more than the other was linked to a larger upper limb representation in the hemisphere contralateral to the hand mostly used (Nudo et al., 1996). Such brain and behavior mapping was shown to be powerful for motor function rehabilitation in stroke patients who lost the use of one arm; the intensive coupled training of the activity of both arms helped function recovery of the hemiparetic arm (Luft et al., 2004; Waller and Whitall, 2005). Together, these studies stress how specific motor activity can drive neuromotor reorganization. But this process of reorganization can go both ways. A study found that practice-dependent neural reorganization can, in turn, shape motor performance (Dorris et al., 2000). Thus, as a whole, these studies point to the constant mapping existing between brain and behavior as new sensory-motor skills are being learned, practiced, and assimilated.

Corbetta and Bojczyk (2002) suspected that a similar kind of mapping could have occurred between the emergence of novel forms of locomotion, reaching patterning, and the brain. When infants learn new fundamental motor skills such as crawling or walking, they need to learn how to use their body in a new way (Adolph et al., 1998; Kubo and Ulrich, 2006; Snapp-Childs and Corbetta, 2009). This involves coordinating and sequencing complex sets of muscles in a manner they never performed before. We also know that when infants discover how to use their body to achieve these new skills, they tend to practice them a lot (Adolph et al., 2012). Corbetta and Bojczyk (2002) reasoned that it was the specific and extensive practice of novel arm activity used in the context of learning these new locomotor skills (i.e., to control balance or generate new limb sequences) that temporarily transferred to reaching via brain functional reorganization. During such critical periods of motor skill learning, the brain is attempting the difficult task of integrating novel and complex forms of movement coordination into the existing motor repertoire of the child. It is possible that this type of sensory-motor integration process is initially achieved by temporarily mapping a novel functional use of some sets of muscles and limbs in some tasks (i.e., locomotion) with prior existing functional uses of these same sets of muscles and limbs in other tasks (i.e., reaching). Such mapping could lead to a period of temporary, undifferentiated responses across tasks in the process of integrating the new skill in the existing motor repertoire of the child. Differentiation between skills would progressively take place as mastery and control of the new emerging skills would form. In walking, for example, the upper arm coupling adopted during the first weeks of upright locomotion (Ledebt, 2001; Corbetta and Bojczyk, 2002) may become a preferred mode of arm use for children, due to their poor upright balance control and extensive practice at coupling their arms during stepping (Kubo and Ulrich, 2006). This increase in upper arm coupling may be mapped onto the corresponding cortical sensory-motor areas controlling the upper arms, thus driving an increased cortical representation of arm coupling during this period of learning. In turn, this representation could be transferred or mapped onto the same set of muscles during reaching, even though infants are not walking, but sitting while reaching, and have reached using different patterns prior to the onset of upright locomotion. Thus, combining identical groups of muscles in similar functional ways across tasks and behaviors could be a temporary solution to facilitate the sensory-motor integration

of the new motor skill into the existing motor repertoire of the child. Consistent with such interpretation, Corbetta and Bojczyk (2002) observed that infants maintained coupling in seated reaching as long as they were coupling their arms following the onset of independent walking. When infants improved upright balance control, lowered their arms, and decoupled them, coupling in reaching declined as well.

The same scenario could be applied to the transition to hands-and-knees crawling. When infants are learning to crawl on hands and knees, they figure out how to sequence and alternate arms and legs in order to move their body forward. As they do so, both arms acquire the new role of supporting the body. In that role also, both arms become equally preferred, but in an alternate way, since they are both used sequentially to move the body forward. Thus, as infants learn to crawl on hands and knees, the activities of the arms remain uncoupled but are used in alternation. Consistent with such scenario, Corbetta and Thelen (1999, 2002) found that such uncoupled, alternated, and distributed preferred hand use became the more predominant mode of response in reaching when infants began to practice hands-and-knees crawling. Thus again, the similarity and consistency of patterns of arm use across crawling and reaching could be the result of a temporary, undifferentiated mapping between the brain functionally reorganizing to assimilate the new locomotor skill while maintaining reaching, especially given that both tasks require the use of similar upper arm sets of muscles.

This interpretation that newly practiced patterns of hand use following the emergence of novel forms of locomotion can transfer to reaching was further generalized to other skills through the longitudinal study of two young infants that adopted less common forms of self-produced locomotion (Corbetta et al., 2006). One child, who began to locomote by scooting on his buttocks while in a sitting posture, also began to couple his arms during reaching over the same developmental period. As in prior reports, the rise in reaching coupling that occurred following the emergence of scooting was interpreted as a result of the emergent upper arm coupling that was extensively performed during scooting. Another infant, who, in contrast, preferred to crawl on his belly by dragging his body on the floor by using the same steady, lateralized pattern between hands and legs continued to maintain a strong right hand use for reaching. Unlike other infants who alternated arms for crawling on hands and knees and displayed a disappearance in hand preference, this infant maintained a strong right bias in reaching, presumably as the result of never alternating arm movements during belly crawling. Thus, these two case studies not only confirmed that hand patterns during reaching can reciprocate arm patterns used during specific learning of forms of locomotion but also showed that mapping between arm use during locomotor and reaching tasks can generalize across multiple and varied forms of locomotion.

The goal of this study was to test our hypothesis that functional brain reorganization may underlie the above documented changes and transfer in hand use across locomotor skill learning and goal-directed reaching. We mentioned above that the neuroscience literature offers supportive evidence for such activity-dependent cortical reorganization, but these studies were performed with human adults or animals. Evidence from the human infant literature revealing the occurrence of such activity-dependent brain reorganizations is quite sparse. To our knowledge, the only study that supports such experience-dependent cortical reorganization in early normal development was performed by Bell and Fox (1996) in which they documented changes in Electroencephalogram (EEG) coherence in four groups of 8-month-old infants that differed in their levels of crawling experience. EEG coherence is the frequency-dependent, squared cross-correlation of electrical signals between two scalp electrode sites (Nunez, 1981; Thatcher et al., 1986). Coherence values range from 0 to 1 and Thatcher proposed that coherence indicates the strength and number of synaptic connections (Thatcher, 1994) and, thus, is reflective of the level of connectivity between two cortical sites. High coherence values indicate that cortical regions are intricately linked and working together. Greater connectivity during development, however, does not always indicate greater maturity. At an early period in development, high coherence values may indicate that two distant cortical regions are intricately linked and working together. With maturation, there may be increased regional differentiation and a decrease in coherence. Thus, measures of EEG coherence can be used to investigate early developmental changes in cortical organization or structural connectivity (Bell, 2001, 2012). Furthermore, EEG coherence has been successfully employed by researchers to capture change in brain connectivity between electrode sites as a function of change in coupling between effectors during the motor learning of bimanual tasks in adults and children (e.g., Andres et al., 1999; Serrien and Brown, 2003; de Castelnau et al., 2008).

Bell and Fox (1996) reported an inverted U-shaped function in EEG coherence as a function of increasing crawling experience. Based on resting baseline measures of brain electrical activity, the novice crawlers (with 1–8 weeks experience) displayed greater EEG coherence than either the pre-crawling group or the experienced crawlers. Particularly, changes in EEG coherence were found over the medial frontal/lateral frontal and medial frontal/occipital regions. Bell and Fox interpreted the increase in EEG coherence in novice crawlers as reflecting an increase in synaptic connections between brain sites associated with onset and early experience at crawling. They considered the decrease in EEG coherence in the most experienced crawlers as reflecting a pruning of the over-abundant synaptic connections when crawling became more skilled.

Our study aimed to extend the work of Bell and Fox (1996) by examining whether similar changes in EEG coherence could be captured during the transition to upright locomotion in 12-month-old infants, and examine if these changes mapped onto changes in reaching. As in Bell and Fox (1996), we used groups of infants that were age matched but had distinct levels of walking experience (non-walkers, novice walkers, and more experienced walkers) and, as in Corbetta and Bojczyk (2002), we examined these infants' reaching skills while they were supported in a sitting posture and reaching for small objects presented at midline. With the goal of addressing the issue of transfer of learning discussed above, we predicted, based on Bell and Fox (1996), that novice

walkers who are coupling their arms during walking would display increased EEG coherence in resting baseline brain electrical activity relative to prewalking infants. We expected that cortical regions in support of gross motor behaviors related to walking would be linked and working together in the early performance of this newly acquired skill. We also predicted that such increased arm coupling during walking in novice walkers should also occur in reaching while seated, and should result in a lower manual laterality index during reaching (Corbetta and Bojczyk, 2002; Corbetta and Thelen, 2002; Berger et al., 2011). We also hypothesized that as infants acquired experience with walking and decoupled their arms during walking, EEG coherence would decrease as overabundant synapses would be pruned due to increased regional differentiation. Coupling in reaching would also decline, and as a result of arm decoupling, manual laterality would increase.

Finally, because the cortical reorganization we aimed to examine is in relation to increased upper arm coupling of homologous muscles in novice walkers, we predicted that increased EEG coherence should occur in homologous sites of the brain hemispheres. We also had hypotheses about specific brain areas. The motor cortex of the frontal lobes is involved in the planning and execution of movement, such as walking and reaching, but more anterior frontal areas are associated with reaching as well. Using near-infrared spectroscopy with adults, Goto et al. (2011) reported that the lateral prefrontal cortex was involved in reaching that was both perceptually consistent and perceptually effortful. Wallis et al. (2001) demonstrated that monkeys with lesions to the lateral prefrontal cortex had difficulty transferring reaching strategy to a new context. Finally, using EEG, Cochin et al. (1999) reported mu rhythm synchronization at lateral frontal and motor cortex electrode sites, along with some temporal and parietal locations, during observation as well as execution of finger movements. Using the classic 10/20 system of electrode classification, the lateral frontal electrode locations are F7, F8 and the motor cortex locations are (central) C3, C4. Thus, we specifically examined changes in EEG coherence during resting baseline in homologous lateral frontal and motor cortex (F7/C3, F8/C4). Because of the linkages between changing reaching patterns with onset of walking, we hypothesized that novice walkers would show increased frontal/central coherence during resting baseline compared to pre-walking or experienced walkers of the same age.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 50 healthy, 12-month-old infants (26 boys and 24 girls) who were recruited from birth announcements placed in the local newspaper. Approximately half of the infants were also participating in a longitudinal study of individual differences in cognitive development and had been in the research laboratory at 5 and 10 months of age for that study (e.g., Diaz and Bell, 2011; Cuevas and Bell, 2013; Kraybill and Bell, 2013). Infants were 96% Caucasian and all parents had a minimum of a high-school diploma. Infants were born within three weeks of their expected due dates and were seen within three weeks following their 12-month birthday, with the exception of one infant who was seen within four weeks. Infants were given a t-shirt or a book for their participation in the study. This study was approved by the Virginia Tech Institutional Review Board.

PROCEDURES

Upon arrival at the research laboratory, parents were shown the electrophysiological equipment and all research procedures were explained. After obtaining written parental consent, EEG electrodes were applied and the different tasks were performed in the following order: first, a 1-min baseline physiology was recorded while the infant was sitting on the mother's lap, then reaching while sitting was assessed (the electrodes remained on the scalp during the reaching task), and finally, after removing the EEG cap, infants were encouraged to walk along a corridor to assess their level of self-produced locomotor experience. This task order was chosen and maintained to control for potential lingering effects of arm coupling in reaching and/or walking on EEG coherence and arm coupling of walking on reaching.

EEG recording

EEG recordings were accomplished during baseline and during a reaching task. We focus on the baseline EEG data in this report. Recordings were made from frontal pole (Fp1, Fp2), medial frontal (F3, F4), lateral frontal (F7, F8), central (C3, C4), parietal (P3, P4), and occipital (O1,O2) scalp locations. All electrode sites were referenced to Cz during recording. Baseline EEG was recorded for 1 min while the infant sat on the mother's lap. During the baseline recording, a research assistant blew on a toy pinwheel to make it spin, 1.1 m in front of the infant. This procedure quieted the infant and yielded minimal eye movements and gross motor movements, thus allowing the infant to tolerate the EEG cap for the recording. Mothers were instructed not to talk to their infants during the EEG recording. Immediately after baseline, the reaching task was administered.

EEG was recorded using a stretch cap (Electro-Cap, Inc., Eaton, OH, USA) with electrodes in the 10/20 system pattern. After the cap was placed on the infant's head, recommended procedures regarding EEG data collection with infants and young children were followed (Pivik et al., 1993). Specifically, a small amount of abrasive gel was placed into each recording site and the scalp was gently rubbed. Following this, conductive gel was placed in each site. Electrode impedances were measured and accepted if they were below 10 K ohms.

The electrical activity from each lead was amplified using separate SA Instrumentation Bioamps (San Diego, CA, USA) and bandpassed from 0.1 to 100 Hz. Activity for each lead was displayed on the monitor of an acquisition computer. The EEG signal was digitized on line at 512 samples per second for each channel so that the data were not affected by aliasing. The acquisition software was Snapshot-Snapstream (HEM Data Corp., Southfield, MI, USA) and the raw data were stored for later analyses. Prior to the recording of each subject a 10 Hz, 50 μV peak-to-peak sine wave was input through each amplifier. This calibration signal was digitized for 30 s and stored for subsequent analysis.

Spectral analysis of the calibration signal and computation of power at the 9–11 Hz frequency band was accomplished. The power figures were used to calibrate the power derived from

the subsequent spectral analysis of the EEG. EEG data were examined and analyzed using the EEG Analysis System software developed by James Long Company (Caroga Lake, NY, USA). First, the data were re-referenced via software to an average reference configuration (Lehmann, 1987). The average reference configuration requires that a sufficient number of electrodes be sampled and that these electrodes be evenly distributed across the scalp. Luck (2005) has demonstrated with event-related potential recordings that voltage can be affected by average reference montage when only mid-line electrodes, as opposed to an entire scalp of electrodes, are used. Currently, there is no agreement concerning the appropriate number of electrodes (Davidson et al., 2000; Hagemann et al., 2001; Luck, 2005). Average referencing is considered the optimal configuration when computing coherence between spatially distinct electrodes (Fein et al., 1988). Then, average reference EEG data were artifact scored for eye movements using a peak-to-peak criterion of 100 μV or greater. Artifact associated with gross motor movements over 200 μV peak to peak was also scored. These artifact-scored epochs were eliminated from all subsequent analyses. The data then were analyzed with a discrete Fourier transform (DFT) using a Hanning window of one-second width and 50% overlap. Power was computed for the 6–9 Hz frequency band because infants have a dominant frequency between 6 and 9 Hz (Bell and Fox, 1992; Marshall et al., 2002). Coherence between electrode sites within each hemisphere was computed using an algorithm by Saltzberg et al. (1986). Coherence calculations were performed by averaging the normalized complex cross-spectral density within the 6–9 Hz frequency band across the baseline recording period. Each individual frequency was uniformly weighted within 6–9 Hz band (Saltzberg et al., 1986, Eq. 9). Based on the literature, we focused on EEG coherence between lateral frontal and central scalp locations in both hemispheres (F7/C3, F8/C4).

Reaching task

Immediately after baseline physiology recording, the reaching task was administered (Corbetta and Bojczyk, 2002). An experimenter sitting in front of the child removed a toy from under a cover and presented it to the child while saying, e.g., "Look! It's a frog. Do you want it?" The toy was held for a few seconds out of the infant reach, at infant's shoulder level, and then moved forward in a straight horizontal path to the infant reaching space while saying "Here, it comes!" followed by the infant reaching. Once the infant had grasped the object, she was given time to explore the object, then, the object was taken away, hidden under the cover, and a new trial began with a new toy. From toy presentation to toy removal, a trial lasted typically about 30 s. Objects for reaching were small toys (balls, animals, rattles, 4–5cm diameter) that infants could easily grasp with one hand. They were presented one at a time, at mid-line, and at infants' shoulder height. Ten to 11 trials were collected, then the EEG electrode cap was removed and the infant was accompanied in a corridor adjacent to the EEG testing room for walking assessment (see below). The reaching session was videotaped for further behavioral analyses using one single video camera, located at 45° angle on the front left side of the child, allowing visibility of both reaching hand.

Reaching responses were coded from the videos as right, left, or bimanual depending on the arm (R or L) and number of arms (1 or 2) that were extended toward the object during reaching (Corbetta and Thelen, 1996). Right and left codes were used for unimanual arm responses when only one arm (the right or the left) was used to reach for the object. For this code, the non-reaching contralateral arm was not active during the reaching action of the other arm and most commonly remained on the side of the infant body. The bimanual code was used to capture reaching responses in which both arms were coupled in their extension toward the object. Timing between the onset/offset of the arm movements could vary, but movement extensions of both arms toward the target had to overlap during most of the transport duration of the hands toward the target to be coded as bimanual. If one arm reached first, and the second arm began to reach immediately after the first hand had already contacted the target (as in alternated patterns), this response was coded as unimanual, as it did not reflect spatio-temporal coupling between arm movements. Inter-rater reliability for reaching coding was 96.84%. From these data, we computed two variables per infant: (1) a percentage of bimanual responses, which was the number of bimanual reaches divided by the total number of reaching trials performed, and (2) and index of manual laterality was computed using the following equation: $(\frac{(R+(B/2))-(L+(B/2))}{R+L+B})$, where bimanual reaches were split between arms (see Corbetta and Bojczyk, 2002; Jacobsohn et al., 2014).

Locomotor assessment

For the last part of the testing, infants were engaged in play activities in a 6-m-long corridor aimed at enticing and capturing their locomotor skills. The mother placed her infant at one end of the corridor, then walked to the other end of the corridor, and encouraged her infant to come. Mothers endorsed that the infants' choice of locomotion toward them (walking, crawling) was the child's preferred mode of locomotion. As with the rest of the laboratory visit, the locomotor session was videotaped for further behavioral analyses. Based on the filmed locomotor assessment, infants were assigned to one of the three groups depending on their walking skills and arm coupling during walking: not walking yet ($n = 18$, age average = 12.10 (months/days), SD = 0.013), novice walkers ($n = 17$, age average = 12.05 (months/days), SD = 0.044), and more experienced walkers ($n = 8$, age average 12.09 (months/days), SD = 0.019). Definition of the novice walkers and experienced walkers categories was based on the arm position infants used during walking (as in Corbetta and Bojczyk, 2002). Novice walkers were those infants walking with their arms coupled in high guard position, i.e., above infant waist level. The experienced walkers were those infants walking with their arms decoupled at or below waist level. Reliability coding of walking level and arms position during walking performed on 39% of the infant sample yielded a 100% agreement. Statistical testing confirmed that there were no significant age difference between groups after performing the above classification based on walking experience [Kruskal–Wallis $\chi^2(2) = 1.070$, $p > 0.586$].

Complete data for analyses

EEG data were available for 43 of the 50 infants (23 boys and 20 girls). Data were lost for seven infants: one due to bioamp

failure, one due to extraneous electrical interference in the EEG signal, two due to heart rate interference in the EEG signal, two due to excessive fussiness/crying, and one because both raw and transformed power values were more than 3 SD below the mean of this group of infants. Also, of the 50 infants, 47 of them provided reaching data. One infant refused to reach for the objects and there were technical difficulties with the video recording for two infants. Locomotor assessment was obtained for all 50 infants.

RESULTS

BASELINE EEG COHERENCE

We performed repeated-measures MANOVA on the EEG coherence data recorded during baseline. Based on our hypotheses, we focused on the homologous lateral frontal/central coherence pairs (F7/C3, F8/C4). Hemisphere was the within-subjects factor and walking group was the between-subjects factor. There was a main effect for walking group, $F(1,40) = 3.367$, $p = 0.045$, and a main effect of hemisphere, *Wilks* $= 0.906$, approximate $F(1,40) = 4.172$, $p = 0.048$. The group by hemisphere interaction was not significant ($p = 0.124$). *Post hoc* analyses were done to determine which groups differed with respect to frontal/central coherence. As seen in **Figure 1**, non-walkers and novice walkers differed in EEG coherence ($p = 0.001$), novice and experienced walkers differed ($p = 0.005$); however, there was no difference in EEG coherence values between the non-walker and experienced walker groups ($p = 0.246$). Thus, the novice walkers had the greatest EEG coherence values and this change occurred on both homologous sites.

To assess whether changes in EEG coherence as a function of walking experience were solely limited to the predicted lateral frontal/central pairs (F7/C3, F8/C4), we ran additional hemisphere × group repeated-measures MANOVAs on all other electrode pair combinations. These analyses revealed no other significant changes in EEG coherence as a function of walking experience (all p's > 0.07).

We also examined whether these walking group differences in EEG coherence were accompanied by group differences in EEG spectral power. MANOVA analysis of the electrodes of interest (F7, F8, C3, C4) revealed no main effects or interactions with walking group (all p's > 0.70). This suggests that cortical activation at medial frontal and central scalp locations was similar for the three walking groups.

COUPLING AND LATERALITY IN REACHING

A Kruskal–Wallis test performed on the percent of bimanual reaching responses of the three walking groups revealed no significant group differences ($p > 0.471$). **Figure 2** shows that the rate of bimanual reaching followed the predicted trend of a higher value in the novice walker group, but even pairwise comparisons testing did not reveal significant differences between groups (all Mann–Whitney p's > 0.175).

The laterality index, on the contrary, revealed strong group differences that were consistent with our predictions. **Figure 3** shows that reaching laterality (specifically right hand use) was significantly greater for the experienced walker groups compared to the two other groups (Kruskal–Wallis χ^2 (2) $= 6.587$, $p = 0.037$). Follow-up pairwise group comparisons confirmed that the experienced walkers used their right hand for reaching significantly more than both the novice walkers [Mann–Whiney $U = 32.50$, $p = 0.015$ (two-tailed)] and non-walkers [Mann–Whiney $U = 33.00$, $p = 0.022$ (two-tailed)]. The non-walkers and novice walkers did not differ from each other in their preferred hand use ($p > 0.966$) and both revealed laterality indexes that were close to 0.

DISCUSSION

The goal of this research was threefold: first, we wanted to assess whether novice walkers who are coupling their arms in the

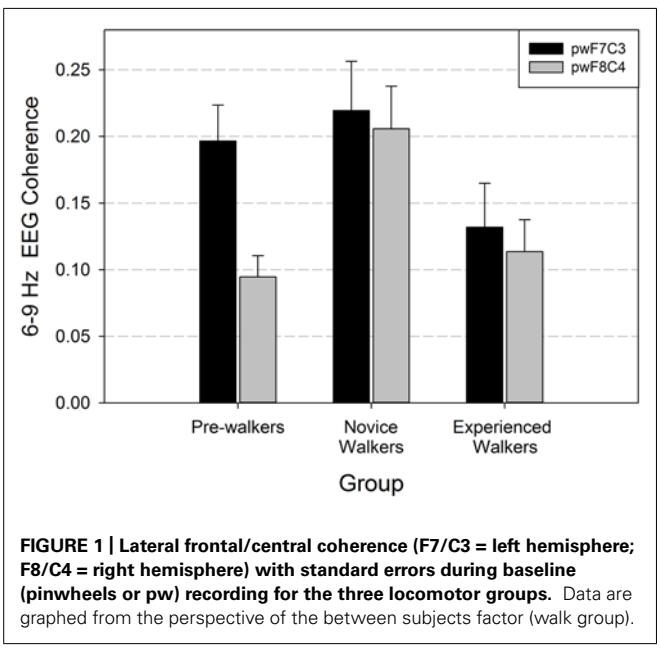


FIGURE 1 | Lateral frontal/central coherence (F7/C3 = left hemisphere; F8/C4 = right hemisphere) with standard errors during baseline (pinwheels or pw) recording for the three locomotor groups. Data are graphed from the perspective of the between subjects factor (walk group).

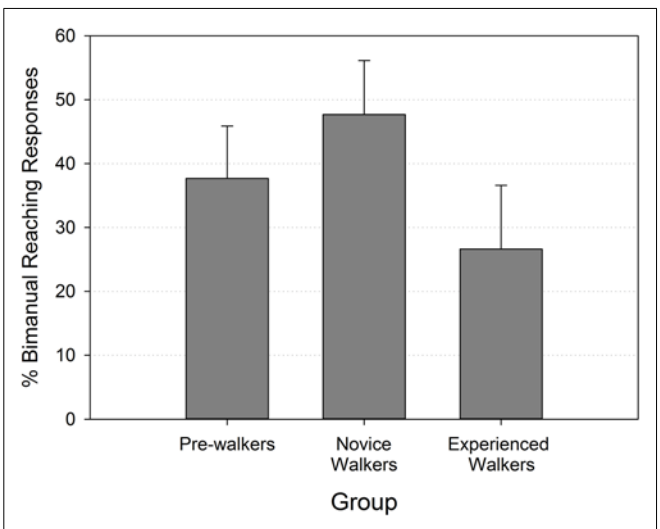


FIGURE 2 | Mean percentages of bimanual reaching responses (with standard errors) by walking group.

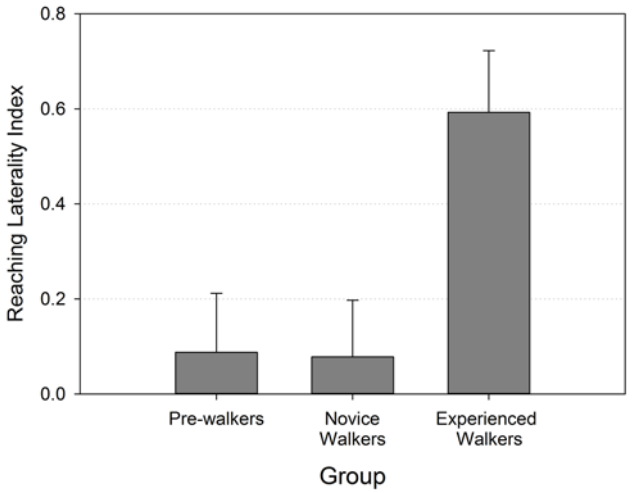


FIGURE 3 | Reaching laterality index (with standard errors) by walking group.

early stages of learning to walk would display increased structural EEG coherence in resting baseline brain electrical activity relative to same age prewalking infants and more experienced walkers who are not coupling their arms as much for self-produced locomotion. Second, we wanted to assess whether differences in structural EEG coherence would occur bilaterally in homologous brain sites and specifically in brain areas that have been associated with motor planning and motor execution [i.e., motor areas (C3/C4) and lateral frontal areas (F7/F8)]. And third, we wanted to assess whether different levels of walking experience and their associated levels of EEG coherence would also map onto infants' arm coupling and manual laterality during seated reaching. This last goal was aimed at assessing our hypothesis on transfer of learning from walking to reaching in relation to the increase in bimanual coupling and decrease in manual laterality documented by prior studies at the time infants are learning to walk (Corbetta and Bojczyk, 2002; Berger et al., 2011; Babik et al., 2014).

The majority of our results were consistent with the predictions we made in relation to those three goals. First, we observed an increase between pre- and novice walkers and a decrease between novice and more experienced walkers in structural resting EEG coherence. Recall that all infants in the study were the same age to minimize age confound in our data and to focus more readily on differences in self-produced locomotor experience between groups. This EEG coherence pattern across groups replicated and extended prior findings from Bell and Fox (1996) who reported a similar, inverted U-shaped pattern in EEG coherence in relation to the infants' crawling experience. Thus, these data show that the emergence of novel and distinct gross motor milestones occurring at different periods of early development are repeatedly associated with patterns of cortical reorganizations and changes in brain connectivity. In the Bell and Fox (1996) and this study, increase in EEG coherence (and assumed increase in synaptic connectivity across brain sites) was found in the novice motor learners, during periods of critical skill development, but not in the premotor learner and the more experienced motor performers.

It should be noted that the coherence findings in our study could be affected by volume conduction (i.e., cortical activity recorded at one scalp location contributing to the signal at other nearby scalp locations). There is evidence, however, that volume conduction effects are much smaller in infants than adults because of their thinner skulls (Grieve et al., 2003). Furthermore, as there were no differences in EEG spectral power across walking groups, it is unclear whether volume conduction differences across groups would have affected the findings.

Second, in this study and as we predicted, the observed change in EEG coherence associated with early walking occurred across homologous motor and lateral frontal brain sites in relation to arm coupling during walking. Recall that the pre, novice, and more experienced walker groups were defined as a function of the infant arm coupling observed during walking. This particular finding met our expectations of how, where in the brain, and in which group increase in EEG coherence should have occurred, and is consistent with our hypothesis that such bilateral structural cortical reorganization may reflect the greater arm coupling practiced during the initial period following the emergence of independent, bipedal walking.

The last results only partially met our predictions. They concerned the coupling and laterality patterns of goal-directed reaching that were actually produced by the infants. According to our hypothesis on transfer of learning, and in line with prior findings from longitudinal studies (Corbetta and Bojczyk, 2002; Berger et al., 2011; Babik et al., 2014), we also expected greater bimanual reaching in the novice walker group compared to the two other infant groups. Furthermore, we expected lower manual laterality in the prewalker and novice walker groups compared to the more experienced walkers. As discussed in the section "Introduction", prewalking infants are more likely to alternate arm use during hands-and-knees crawling, and novice walkers are more likely to couple their arms during walking, both of which were found to correspond to lower levels of lateralized hand use in reaching compared to more experienced walkers (Corbetta and Thelen, 2002; Berger et al., 2011). We found a weak, non-significant increase in arm coupling in the novice walker group but verified the predicted increase in manual laterality trends as a function of the locomotor experience groups. We think that this partial support of our transfer of learning hypothesis can easily be explained by the cross-sectional study design that we adopted for the purpose of this study, which was aimed at comparing EEG coherence in same-aged infants, albeit with different skills.

All the studies that reported a link between changes in arm use in reaching as a function of emerging locomotor skills used longitudinal designs (Corbetta and Bojczyk, 2002; Corbetta and Thelen, 2002; Corbetta et al., 2006; Berger et al., 2011; Babik et al., 2014). Longitudinal designs allowed researchers to identify change in behavior over time more accurately despite wide individual differences in skill onsets and notable variations in developmental trajectories (see Corbetta and Bojczyk, 2002; Berger et al., 2011; Jacobsohn et al., 2014). What makes increases (or declines) in bimanual reaching following the onsets of locomotor skills

particularly identifiable is the change in baseline behavior over several weeks in a row. These changes in baseline behavior can be identified despite the week-to-week or day-to-day fluctuations that are typical of infant behaviors. Thus, the observed increase in arm coupling, or decline in manual preference, as those reported by prior studies, are compound results obtained over several weeks of behavioral observation and therefore are more likely to demonstrate more consistent trends across infants over the observed period. Thus, longitudinal designs allowed researchers to capture the regularities across infant behavioral changes more reliably despite the high response variability intrinsic to infant behavior.

These advantages are not present when behaviors are observed over one single session, as in this study. Single-session observations are more likely to be subject to data inconsistencies due to fluctuation in behavior over time and time of sampling. Prior longitudinal studies that displayed changes in bimanual and lateral reaching in infants over extended periods of time have shown how unstable and fluctuating the week to week infant reaching patterns can be, despite periods of identifiable behavioral trends (see Corbetta and Thelen, 1996, 1999; Corbetta and Bojczyk, 2002). Thus, depending on the day the data were collected, results may not always reflect the overall trend of increased arm coupling in reaching that would be observed if the behavior were observed over several weeks in a row following the onset of the transition skill.

Measuring arm coupling in infant reaching is another source of data variability. Movement lag variability in infant bimanual reaching can be quite significant, even during periods of predominant bimanual reaching (see Corbetta and Thelen, 1996). Finally, a couple of recent studies have suggested that increased coupling in infant reaching may actually begin to occur in some infants before the onset of upright locomotion. Thurman et al. (2012) observed that the timing of the increase in bimanual reaching in six infants followed longitudinally was more in in line with the onset of standing alone than walking *per se.* And, Atun-Einy et al. (2014) found that increase in bimanual reaching began to show a small rise when infants began cruising. Thus, there may be several reasons for our lack of finding of the predicted significant increase in bimanual reaching in the novice walker group. Namely, the high intra- and interindividual response variability inherent to infant reaching can more readily affect data collected over a single day. And the fact that bimanual reaching may already occur in prewalking infants when standing and cruising could contribute to reducing the expected significant increase in reaching coupling from pre- to novice walkers.

IMPLICATIONS FOR THE DEVELOPMENT OF MANUAL LATERALITY

Overall, findings from this study continue to counter the view that the development of hand preference in infancy follows a set or a steady developmental progression over time. Rather, data from this research continue to support a more plastic, more malleable view of the development of early hand preference, a view involving a process of complex interactions and integration between multiple developmental systems (i.e., whole body gross motor reorganization, structural and functional cortical reorganization, and goal-directed reaching; Corbetta et al., 2006; Corbetta, 2009). This research is also novel in assessing and linking specific aspects of behavioral learning (i.e., locomotion) and the concomitant behavioral reorganization of prior existing skills (i.e., reaching) with predicted changes in the brain. We think that these documented changes in both behavioral and electrophysiological levels as a function of walking experience are important for our understanding of the development of infant manual laterality.

There is some consensus in the field of developmental laterality that manual preference is not clearly established until the age of 2 or 3 years olds (e.g., McManus et al., 1988; although see Michel, 1981). We have argued in previous work that one reason why infants display highly fluctuating patterns of hand preference in the first years of life is related to the multiple and successive postural reorganizations that infants incur and need to acquire on their way to mastering the upright bipedal locomotion (Corbetta and Thelen, 2002; Corbetta, 2005; Corbetta et al., 2006). Since upright locomotion marks the last step of several gross motor reorganizations in early development, growing and more stable trends in hand use preference should begin to appear after the skill of walking has become more stable and more routine. Furthermore, from this time, infants arms are free from their gross locomotor supporting role (as in crawling), or balance control role (as in sitting or walking), which in turn should contribute to the development of more specific and more differentiated arm and hand use to achieve a greater variety of tasks. We found such increase in manual laterality following the onset of upright locomotion in a longitudinal study (Corbetta and Thelen, 2002). And there are several data from the developmental literature showing a steadier growing of manual laterality in the second year of life as infants engage in more dexterous manual tasks (i.e., Fagard and Marks, 2000; Jacobsohn et al., 2014) and tool use (Kahrs et al., 2013; Rat-Fischer et al., 2013). Increased manual laterality in relation to adopting an upright posture or bipedality has also been found in non-human primates and other mammals that typically do not display preferred hand use at the population level (Giljov et al., 2012; see also Corbetta, 2005, for a review of the non-human primate literature on posture and manual laterality). Thus, a link between the acquisition of the upright posture and the expression of manual laterality has been documented across development and across species. Our data on infant reaching laterality as a function of walking experience groups are consistent with this scenario. The predicted significant increase in manual laterality was found only in the more experienced walking group, which was the group holding their arms at or below waist level during walking, meaning that they were not relying on their arms so heavily anymore to control balance and moving forward (Ledebt, 2001; Kubo and Ulrich, 2006; Snapp-Childs and Corbetta, 2009). The increase in reaching laterality in that experienced group was also associated with a decrease in EEG coherence, and thus increased regional differentiation in the brain. We could not detect systematic brain asymmetries with our EEG measures (especially to tease apart brain patterns between low lateralized prewalking infants and more lateralized experienced walkers), but future developmental studies should be designed to capture functional brain asymmetries in reaching in toddlers as a function of established hand preference patterns. If we are correct in our assumptions that manual laterality becomes more

established after the onset and mastery of upright locomotion, we should discern more distinct lateralized brain response in reaching after experience with upright locomotion compared to developmental periods when upright locomotion has not yet been stably acquired.

Another limitation is that our study was cross-sectional. Because this was a first investigative study of our hypothesis of transfer of learning, we chose to control age in order to be able to compare mapping levels between EEG coherence and behavior as a function walking experience. But cross-sectional approaches only offer a snapshot of unique moments of development, and therefore they are limited when trying to account for the processes that are driving change over time. Because of our design, we cannot infer how the documented changes in EEG coherence can predict or have led to the formation of the new lateralized manual organization found in the experienced walkers. Furthermore, other physiological measures beyond structural EEG coherence should be used to attempt to capture the active brain processes that might be involved in this process of lateralization. In prior work, we argued that preferred hand use develops from a background of repeated fluctuations in behavior, where stabilization and selection of specific patterns of response form as the result of progressive cumulated experiences (Corbetta et al., 2006; Jacobsohn et al., 2014). But to further these issues and better understand how such patterns of lateralization form over time, we need to conduct longitudinal studies that integrate brain and behavioral measures.

Overall, our work confirmed the changing nature of the development of early hand preference, in particular in relation to the development of novel locomotor skills. Our data on the EEG coherence verified and extended Bell and Fox (1996) original findings that each change in motor skills learning is accompanied by changes in brain cortical reorganizations. Over the past decades, neuroscience research has revealed many compelling cases of such brain and behavior mapping and reorganization, but the vast majority of these studies were performed in adults or animals. Here, we show that such mapping across brain and behavioral levels also occur during infancy.

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Hemispheric asymmetries in word recognition as revealed by the orthographic uniqueness point effect

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The orthographic uniqueness point (OUP) refers to the first letter of a word that, reading from left to right, makes the word unique. It has recently been proposed that OUPs might be relevant in word recognition and their influence could inform the long-lasting debate of whether – and to what extent – printed words are recognized serially or in parallel. The present study represents the first investigation of the neural and behavioral effects of OUP on visual word recognition. Behaviourally, late OUP words were identified faster and more accurately in a lexical decision task. Analysis of event-related potentials demonstrated a hemispheric asymmetry on the N170 component, with the left hemisphere appearing to be more sensitive to the position of the OUP within a word than the right hemisphere. These results suggest that processing of centrally presented words is likely to occur in a partially parallel manner, as an ends-in scanning process.

Keywords: orthographic uniqueness point, visual word recognition, cerebral hemispheres, N170, serial/parallel processing, event-related potential

INTRODUCTION

The orthographic uniqueness point (OUP) of a printed word is the letter position, starting from the left, at which the word is distinguishable from all other words in the mental lexicon. For example, the OUP of "*acrylic*" is four. This reflects the fact that, when reading the word "*acrylic*" from left to right, upon reading the letter "*y*," "*acrylic*" is the only possible remaining match. By the same token, the OUP of "*brother*" is 7 as, at letter position 6, there are still other possible matches such as for example "*brothel*." The OUP of words has been proposed as a major determinant of the moment in time in which words are recognized (Kwantes and Mewhort, 1999). If this proves to be the case, our understanding of how printed material is processed will move forward in an unexpected direction. The evidence to date is unclear since the few studies exploring the effect of OUP on the recognition of single words have shown mixed results.

Kwantes and Mewhort (1999) were the first to study the potential influence of OUP in word naming. They found that, on average, words with early OUPs were named 26 ms faster than words with late OUPs, concluding that visual word recognition proceeds in a highly sequential manner. A few years later Lindell et al. (2003) investigated whether this sequential processing of words could be applied to both hemispheres, since according to some accounts, such as the dual mode hypothesis, only serial mechanisms of word processing are available to the right hemisphere while the left hemisphere is endowed with an extra and efficient parallel processing system (Ellis and Young, 1985; Bub and Lewine, 1988; Ellis et al., 2009). Lindell et al. (2003) presented the same 7-letter early and late OUP words used by Kwantes and Mewhort (1999), to the left and right visual fields (RVFs) within the context of a lexical decision task. They found a 33 ms advantage for early over late OUP words with no interactions leading them to conclude that both hemispheres process words in a serial manner. These findings were replicated in a follow-up study by the same group (Lindell et al., 2005), where they assessed the performance of each of the hemispheres when naming laterally presented early and late OUP words. Early OUP were named faster than late OUP in the LH but not in the RH (Experiment 1), the lack of OUP effect in the RH was attributed to the relatively poor perceptibility of the initial letters of words presented in the left visual field (LVF).

The role that the beginning of words plays on word processing has also been studied in relation to the parafoveal information available during fluent reading. The measure used here has not been the OUP but the degree to which the first three letters of the word constraint the number of potential target words. High-constraint words first letters generate few words (e.g., *tyrant, awkward*) while low-constraint words start with letters shared with many other words (e.g., *climax, scrawny*). Hand et al. (2012) found facilitated processing for parafoveal previewed targets with high constraining initial letters. This is assumed to be related to the fact that, during reading, the perceptual span is such that processing of words is not restricted to the currently fixated word and that processing of a parafoveal word begins before fixation (McConkie and Rayner, 1975). Thus, the processing of high-constraint words was facilitated since they generate fewer target candidates than low-constraint words. Rayner et al. (1982) also demonstrated that an invalid parafoveal preview impaired performance when compared with a valid preview, highlighting the importance of the initial letters in reading. The effect of OUP has also been investigated in relation to the parafoveal preview benefit. Miller et al. (2006) used a sentence boundary reading task with eye-tracking measures. Target words were matched for a range of variables, including frequency of the initial trigram. Three preview conditions were included: no parafoveal preview (e.g., *baby thqjzwp*), partial preview (e.g., *baby girazwp*), and full preview (e.g., *baby giraffe*). It was argued that if words are read in a serial-like manner

an advantage for early OUP targets would be observed, as the extent of the preview (three letters) corresponded with the position of early OUP words. Strikingly, Miller et al. (2006) found no benefit for early OUP words but a small and reliable advantage for late OUP words. This is consistent with findings of a faster processing of low-constraint words (Lima and Inhoff, 1985) and opposite to the pattern of results reported by Kwantes and Mewhort (1999), Lindell et al. (2003, 2005).

Lamberts (2005) argued that a potential account for these mixed results is that the observed OUP effects were confounded with total lexical overlap, a factor controlled in Miller et al.'s (2006) study. Total lexical overlap refers to the number of letters-in-position shared by the target and other words within the lexicon. For example, *house* and *goose* share three letters-in-position in common. In a computational analysis, Lamberts (2005) found that Kwantes and Mewhort's (1999) early OUP stimuli shared four letters-in-position with 19 other words in the database; by contrast, late OUP words shared four letters-in-position with 46 other words. Thus, the OUP effects reported by Kwantes and Mewhort (1999) may have been confounded with the extent to which words with early and late OUPs overlapped with other lexical entries rather than the impact of the position of the uniqueness point. More recently, another measure of lexical overlap has been proposed as a better way of operationalising orthographic similarity. This is the orthographic Levenshtein distance 20 (OLD20) which is a measure of the minimum number of additions, subtractions and substitutions required to produce a word from another (Yarkoni et al., 2008). The OLD20 is calculated on the basis of the words contained in the English Lexicon Project, a database comprising more than 40,000 words (ELP; http://elexicon.wustl.edu/).

In sum, the OUP influence on word processing remains unclear. However, establishing the significance of OUP in word recognition and reading is important because it can have substantial implications for the manner in which these processes are currently understood.

An essential concern when examining the behavioral effects of a given variable is the potential low sensitivity of the measures commonly used [i.e., response times (RTs) and accuracy]. This problem may be particularly pronounced when word recognition is measured within the lexical decision paradigm because it is difficult to determine the extent to which RTs reflect the time taken to identify a word or to reach the lexical decision itself. The growing popularity of the event-related potential (ERP) technique means that more sensitive measures of cognitive performance are available and used in the study of cognitive performance (Luck, 2005).

Thus, the present study is the first investigation of the neural and behavioral basis of the OUP effect for a set of well-controlled, centrally presented words. Thirteen English native speakers were asked to complete a lexical decision task where forty words were manipulated in terms of their OUP position (i.e., 20 early vs. 20 late) while RTs, response accuracy and ERPs were recorded. If the position of the OUP has an effect on the recognition of words, faster and more accurate processing was expected for those words with an early OUP. This is under the understanding that early OUP words narrow down the lexical search before late OUP words do (Kwantes and Mewhort, 1999). In addition, the neural activity at the N170 will be examined as a component that has been shown to be crucial in visual word identification processes (e.g., Brem et al., 2006; Ellis et al., 2009). It was predicted that if early and late OUP words evoke differing patterns of electrical activity, these differences would be particularly evident on the N170 component.

MATERIALS AND METHODS

PARTICIPANTS

Thirteen monolingual, native English-speaking students (five male, eight female) participated in the experiment. All participants were students at Swansea University, had normal or corrected-to-normal vision and were between the ages of 18–25 (mean age: 19) All were rated as strongly right-handed by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants received £15 in return for their participation.

STIMULI

Experimental stimuli were selected from a modified CELEX database (Baayen et al., 1993). The CELEX database was modified by removing items consisting of more than one word, hyphenated items and words suffixed with –s, –es, and –ed. These were removed so that when OUPs were calculated they would not be affected by plurality, e.g., biscuit would not be compared with biscuits. This left 43,371 words for use as potential stimuli. The OUP for each of these words was calculated by sorting into alphabetical order and, for any given word, comparing the number of contiguous letters-in-position shared with both the preceding word and the following word. The larger of the numbers plus one was the OUP.

From the stimuli pool, a total of forty 7-letter words were chosen. Half of the words had an early OUP (average OUP letter position: 3.65) and the other half had a late OUP (average OUP letter position: 7). Thus, for words, there were two experimental conditions: (1) early OUP words and (2) late OUP words. All words were matched in terms of frequency, bigram frequency, number of syllables, lexical overlap and orthographic neighborhood size and OLD20 values (taken from the ELP). A set of forty 7-letter orthographically legal non-words was also selected from the ARC Non-word Database to act as non-word foils in the lexical decision task (Rastle et al., 2002).

PROCEDURE

The experiment began with 12 practice trials (six words and six non-words) different from those used as experimental stimuli. Experimental items were presented once the practice trials were over. Participants were exposed to a total of 80 experimental trials (40 words and 40 non-words) upon which they were required to perform lexical decision. Stimuli presentation was randomized and controlled by an IBM Pentium computer, with a 586 processor and 17 inch SVGA display. Participants sat at a viewing distance of approximately 57cm from the display screen in a comfortable chair with a headrest. The experiment was programmed and implemented using E-Prime (2007) software (Psychology Software Tools, 2007). E-Prime (2007) is an experimental generator package that can produce millisecond precision timing.

All stimuli were presented in lower-case, Arial font, size 14 to ensure words were easily readable. Words appeared white against a blue background to minimize screen flicker. Words were presented at fixation and subtended a visual angle of 2°. The central fixation cross subtended a visual angle of 1°.

Each trial commenced with a fixation cross appearing in the center of the screen for 1000 ms. After presentation of the fixation cross, target items were presented for 180 ms at fixation. The participant's task was to decide, as quickly and as accurately as possible, whether the target stimulus was a real word or not. Participants indicated their responses by pressing a key on a two-key response box. Half of the participants were instructed that the left key indicated a word response and the right key a non-word response. Response keys were reversed for the remaining participants. Once a participant had responded, a message appeared on the screen for 2000 ms indicating that their response had been recorded. Immediately after that, the fixation cross was relit for 1000 ms as the next trial began. The importance of fixating on the cross during the task was emphasized in the pre-experimental instructions, as was the need for speed and accuracy. Participants were also instructed not to blink during trials. During the practice trials, participants were trained in how to time their blinks such that they occurred between experimental trials.

DATA ACQUISITION

The electroencephalogram (EEG) was recorded in an electrically shielded EEG chamber housed within the Department of Psychology, Swansea University, UK. Participants sat in a comfortable seat, at a viewing distance of 57 cm from the screen, and were instructed to refrain from moving, blinking, or making eye movements during experimental trials. Data were recorded from 64 Ag/AgCl electrodes (BioSemi Active II System, BioSemi Systems, Amsterdam, NL) mounted on an electrode cap and arranged according to the extended International 10–20 system. Sampling rate was 500 Hz and a 0.1–30 Hz bandpass filter was applied. Data were converted off-line to the average reference and analyzed using BESA Research 5.3. (BESA GmbH, 2010). Eye movements were not specUpon completion of the experimental testing session, participants performed an eye movement calibration task for use in eye artifact rejection following the method proposed by Berg and Scherg (1991).

DATA PRE-PROCESSING

The continuous EEG for each participant was divided into epochs of 1000 ms in length, beginning 200 ms pre-stimulus onset. Trials contaminated with eye artifacts or with peak-to-peak potential differences larger than 75 μv in any channel were rejected. All epochs were baseline-corrected over the 200 ms pre-stimulus interval and converted to the average reference.

As others (e.g., Schendan and Maher, 2009) standard ERP guidelines were followed to ensure the validity of the analyses (Picton et al., 2000). A criteria of a minimum of 10 artifact free trials per condition was established to ensure that the ERP averages for P1 and N170 were detectable. Grand average ERP curves, plotted for early and late OUP words in each hemisphere electrode group are presented in **Figure 1**.

ANALYSIS

BEHAVIORAL RESULTS

Response times of less than 150 ms or more than 2.5 standard deviations from the mean were treated as outliers and removed from the analysis (4.3% of all trials). Eight percent of responses were participant errors and were rejected from subsequent analyses. Non-words were included in the present experiment so as to make lexical decision possible. As it is not possible to manipulate the OUP of non-words, data for non-words will not be analyzed. Mean RTs, standard deviations and accuracy rates for words and non-words are presented in **Table 1**.

A main effect of OUP was evident in the RT data. Words with a late OUP were recognized significantly faster than those with an early OUP: $F_1(1,12) = 8.94$, MSe = 5479.86, $p < 0.01$, $\eta_p^2 = 0.43$, $F_2(1,38) = 4.41$, MSe = 13816.81, $p < 0.05$, $\eta_p^2 = 0.10$.

In the by-subjects analysis of response accuracy, the advantage for late OUP words was observed again. By-subjects, late OUP

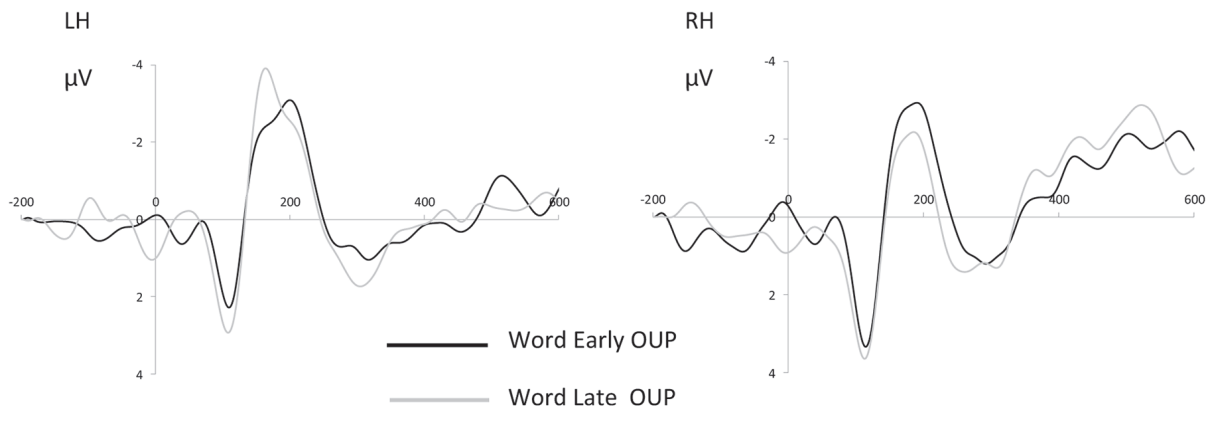


FIGURE 1 | ERP curves for early and late OUP words recordedover the LH (electrode group consisting of P03, P07, P7) and RH (P04, P08, P8). Negative is plotted up. Horizontal axis is in milliseconds.

Table 1 | Mean response times (M), standard deviations (SDs) and percentage accuracy [Acc (%)] as a function of orthographic uniqueness point.

	Words		Non-words
	Early OUP	Late OUP	
M	379	350	379
SD	172	154	142
Acc (%)	78	87	92

Descriptive data for non-words is also presented.

words were recognized more accurately than early OUP words: $F_1(1,12) = 13.45$, MSe = 508.65, $p < 0.005$, $\eta_p^2 = 0.53$. The by-items analysis showed no main effect of OUP on response accuracy.

ERP RESULTS

Only trials with correct responses were included in ERP analyses. Grand average RMS curves, plotted for all conditions across all electrodes, indicated three prominent peaks in the ERP distribution, at ∼100, ∼170, and ∼300 ms post-stimulus onset. Due to the fact that the average RT in the behavioral task was 365 ms the peak occurring at ∼300 was considered to be too close to decision time. Therefore analyses focused on P1 and N170. These components were defined after examining grand average topographies as the maximal positive deflection between 70 and 130 ms (P1) and the maximal negative deflection between 160 and 210 ms (N170) over parietooccipital sites. Analyses were focused on two groups of electrodes, formed from the average of PO3, PO7, and P7 over the left hemisphere and PO4, PO8, and P8 over the right hemisphere. As others (e.g., Schendan and Maher, 2009) standard ERP guidelines were followed to ensure the validity of the analyses (Picton et al., 2000). A criteria of a minimum of 10 artifact free trials per condition was established to ensure that the ERP averages for P1 and N170 were detectable. Grand average ERP curves, plotted for early and late OUP words in each hemisphere electrode group are presented in **Figure 1**. Topographic scalp maps for early and late OUP words are presented in **Figure 2**.

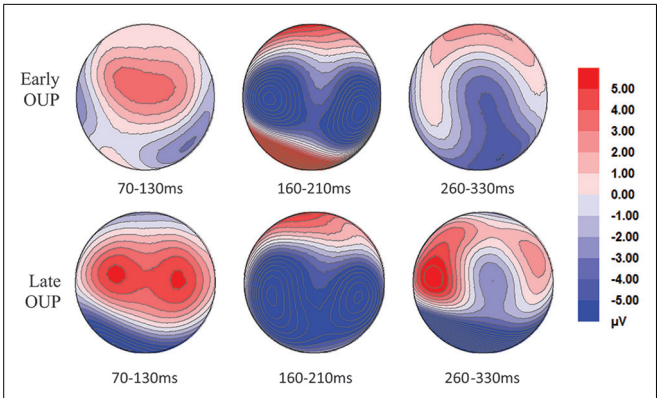


FIGURE 2 | Topographic scalp maps for early and late OUP words.

P1

At 100 ms, amplitudes over the RH were slightly larger than those over the LH, although this effect only approached significance: $F(1,12) = 3.48$, MSe = 4.19, $\eta_p^2 = 0.23$, $p = 0.08$. There was no main effect of OUP: $F(1,12) = 3.01$, MSe = 339.22, $\eta_p^2 = 0.20$, n.s., and no interaction of hemisphere and OUP: $F(1,12) = 2.20$, MSe = 446.32, $\eta_p^2 = 0.16$, n.s.

N170

There were no main effects of either OUP or hemisphere at 170 ms on mean amplitudes. However, these factors interacted: $F(1,12) = 7.84$, MSe = 5.01, $p < 0.05$, $\eta_p^2 = 0.42$. Bonferroni-corrected *post hoc* comparisons were used to determine the nature of the interaction. Early OUP words evoked voltages of equal magnitude in both hemispheres. For late OUP words, amplitudes recorded over the LH (−3.1 μv) were significantly more negative than those recorded over the RH (−1.85 μv; $p = 0.01$). This can be seen in **Figure 1**.

No main effects of OUP or hemispheres were observed in the peak latency analysis. However, OUP and hemisphere interacted again: $F(1,12) = 10.88$, MSe = 961.62, $p < 0.01$, $\eta_p^2 = 0.50$. In the RH, early and late OUP words achieved peak voltage at similar latencies; in the LH, activity evoked by late OUP (174 ms) words peaked significantly faster than that for early OUP words (191 ms; $p = 0.02$).

DISCUSSION

The aim of the present study was to determine the effect of OUP on both behavioral and electrophysiological responses. Participants performed lexical decision on centrally presented letter strings with early and late OUPs whilst EEG recordings were made. Standard behavioral measures of RT and accuracy were obtained, in addition to ERP measures of mean amplitude and peak latency.

The behavioral results are clear: words with a late uniqueness point were recognized faster and more accurately than those with an early uniqueness point. Analysis of ERPs demonstrated differences on the N170 component between early and late OUP words both within and across hemispheres. In the LH, at 170 ms, late OUP words achieved peak latency significantly earlier than early OUP words. Across hemispheres, early OUP words generated equivalent activity in both the LH and the RH, whilst late OUP words generated larger negativities over the LH than the RH at 170 ms.

The results from the experiment presented here are consistent with those of Miller et al. (2006) in suggesting that when words are matched in relevant lexical variables – including total lexical overlap and orthographic similarity (OLD20) – there is a consistent processing advantage for late OUP words over early OUP words. The present results are also in line with other findings such as those observed by Lamberts (2005) in relation to OUP and those reported by Lima and Inhoff (1985) in relation to lexical constraint. The majority of these studies (Lima and Inhoff, 1985; Miller et al., 2006) employed a sentence-reading paradigm where parafoveal information played a crucial role. The results of the current research extend understanding in this area by demonstrating that a facilitatory effect for late OUP words is also found in tasks involving the identification of single words.

The difference between the findings reported here, a 29 ms benefit for late OUP words over early OUP words, and those of Kwantes and Mewhort (1999), who observed a 26 ms advantage for early over late OUP are possibly attributable to the way stimuli were matched in terms of lexical variables. Specifically, stimuli in the present research were matched in terms of the extent to which each target shared four letters-in-position in common with other words following Lamberts (2005) suggestions in addition to be controlled for the more recent measure of orthographic similarity (i.e., OLD20). The results of the present experiment show that when word sets share the same lexical characteristics (e.g., orthographic similarity, frequency) an effect of late OUP words is apparent under conditions of central presentation. Kwantes and Mewhort (1999) account of left-to-right sequential processing of centrally presented words predicts faster recognition times for words with an early OUP. The results of the present experiment do not support such an account.

The present study represents the first electrophysiological evidence of an effect of OUP on neural activity. Interestingly, early and late OUP words generated distinctly different patterns in each of the hemispheres on the N170 component. The behavioral advantage for late OUP words was reflected in the ERP findings in two ways: firstly, in the peak latency analysis, where, in the LH, late OUP words achieved peak latency significantly earlier than early OUP words and, secondly, across hemispheres, where late OUP words generated larger responses over the LH than the RH.

Considering that ERP responses to early OUP words were of equal magnitude in both hemispheres, the behavioral facilitation observed for late OUP words may have been driven by LH activity. This may be due to the fact that, for a late OUP target, the OUP falls to the right of fixation, whereas, for an early OUP target, the OUP falls either at, or slightly left of, fixation. It is well-established that words presented entirely to the RVF are identified faster and more accurately than those in the LVF [see Ellis (2004) for a review]. Studies that explore visual field asymmetries typically displace stimuli between 2 and 3° from fixation (Bourne, 2006), where contralateral stimulation of the hemispheres is assured (subject to suitable experimental control). Traditionally when studies have used a central presentations of words (between 1 and 2°), bilateral projection of the foveal region has been assumed (Garey et al., 1991). Recently, the bilateral representation view has been challenged on the basis of behavioral (e.g., Lavidor et al., 2001; Ellis et al., 2005) and computational evidence (Shillcock et al., 2000) that suggests that information falling in the foveal region is not bilaterally represented but instead the central visual field is split through the vertical midline, with contralateral projection occurring for targets displaced immediately to the left and right of fixation. According to the split fovea theory, the crucial information comprised in the words with late OUPs was being systematically projected to the LH, whereas the information from words with early OUP, which fell at or slightly left of fixation, was projected to either the RH of both hemispheres.

Although the present findings do not support a word recognition account that is strictly sequential, they are neither indicative of a pure parallel processing of printed words. The observed faster responses for late OUP words could be understood as a partial parallel processing that operates in an "ends-in" scanning manner. If analysis of the word is based on an "ends-in" scan, this would mean that a word with an OUP at the last letter (i.e., a late OUP word), would be perceived before than a word with the OUP in the middle of the word (i.e., an early OUP word). This is if we consider that the "ends-in" scanning manner processes the end of the word (and the very beginning) before it gets to the middle.

In addition, the interaction observed in the N170 between OUP and hemispheres indicated a differential hemispheric processing of words with early and late OUPs, with late OUP words showing larger amplitudes and peaking earlier in the left hemisphere. These hemispheric differences shown in the processing of centrally presented words could imply that recognizing words is a hybrid product of the parallel mechanisms argued to reside in the left hemisphere with the more serial processing manner claimed to be characteristic of the right hemisphere (Ellis et al., 2009). Similarly, these findings can also be accommodated within the remits of the SERIOL model and result from differences in the way orthography is encoded in each hemisphere with faster timing of firing of those units initially processed by the LH (Whitney, 2001, 2008).

The present study shows that the issue of the manner of processing in word recognition is complex. The observed differential intervention of the two hemispheres and the processing advantage found for late OUP implies that word recognition might not be operated in a pure serial or parallel manner but as a mixture of both processing mechanisms.

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Task demands modulate decision and eye movement responses in the chimeric face test: examining the right hemisphere processing account

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A large and growing body of work, conducted in both brain-intact and brain-damaged populations, has used the free viewing chimeric face test as a measure of hemispheric dominance for the extraction of emotional information from faces. These studies generally show that normal right-handed individuals tend to perceive chimeric faces as more emotional if the emotional expression is presented on the half of the face to the viewer's left ("left hemiface"). However, the mechanisms underlying this lateralized bias remain unclear. Here, we examine the extent to which this bias is driven by right hemisphere processing advantages vs. default scanning biases in a unique way—by changing task demands. In particular, we compare the original task with one in which right-hemisphere-biased processing cannot provide a decision advantage. Our behavioral and eye movement data are inconsistent with the predictions of a default scanning bias account and support the idea that the left hemiface bias found in the chimeric face test is largely due to strategic use of right hemisphere processing mechanisms.

Keywords: chimeric face test, right hemisphere processing account, scanning bias, eye movements, lateralization of emotion

INTRODUCTION

Hemispheric specialization is a fundamental feature of how the human brain is organized for cognition. Over the past several decades, research has shown that each hemisphere has its own set of capacities and specializations in a variety of domains, including language, spatial processing, and emotional processing (for reviews, see Gazzaniga, 1995; Hervé et al., 2013). Such specializations have been argued to increase the information processing capacity of the brain (Friedman and Polson, 1981; Rogers, 2000) and to allow multiple processing strategies that address computational tradeoffs (e.g., Banich and Belger, 1990; Kosslyn et al., 1992; Federmeier, 2007). However, it remains unclear whether, and, if so, how, the brain can strategically deploy these strategies. Is hemispheric dominance, the tendency for one hemisphere to assume control of processing, fixed for certain forms of information, at least within a given individual? Or are there strategies, such as the deployment of attention to contralateral information, that can be used to flexibly recruit lateralized processing mechanisms for the task at hand (e.g., Levy and Trevarthen, 1976; Hellige and Michimata, 1989; Weissman and Banich, 2000)?

One robust but still incompletely understood metric of hemispheric dominance for face/emotion processing comes from the chimeric face test. This test involves the presentation of chimeric faces, which are vertically split composites of what is usually the same person's face displaying a different expression on each half. For example, in the original version of the paradigm, one side of the hemiface conveys a positive emotional expression (i.e., a person smiling) and the other side a neutral expression (Levy et al., 1983). A chimeric face and its mirror image are presented one above the other (see **Figure 1**, far left), and participants are instructed to indicate which of the two chimeric faces looks happier. Even though the two chimeric faces contain the same information, as one is just a mirror image of the other, neurologically intact right-handed individuals have a tendency to pick the face in which the emotional expression is conveyed on the viewer's left side (the "left hemiface"; for a review and meta-analysis, see Voyer et al., 2012). This left hemiface bias is robust and has been replicated using samples from different cultures (Vaid and Singh, 1989) and age groups (bias emerges as early as 5 years old: Failla et al., 2003) and in versions of the test that make significant modifications to the stimuli. For instance, the use of negative emotional expressions, inverted faces, or cartoon faces may reduce, but do not abolish, the bias (Hoptman and Levy, 1988; Christman and Hackworth, 1993; Luh, 1998; Butler and Harvey, 2005; Parente and Tommasi, 2008; Bourne, 2010, 2011). Furthermore, this left hemiface bias for chimeric faces extends beyond emotional expressions. Other versions of the paradigm in which the differences between the left and right side of the faces are based on age, sex, or attractiveness have also been shown to elicit a left hemiface decision bias (Luh et al., 1991; Burt and Perrett, 1997). These biases are reflected in reaction times as well as decision proportions: participants are generally faster to respond on trials in which they pick the left hemiface than those in which they pick the right hemiface (Bourne, 2008).

A prevailing explanation for the bias observed in the chimeric face test is that the results reflect a right hemisphere dominance for extracting information from faces, perhaps especially emotional information (Voyer et al., 2012). Some of the

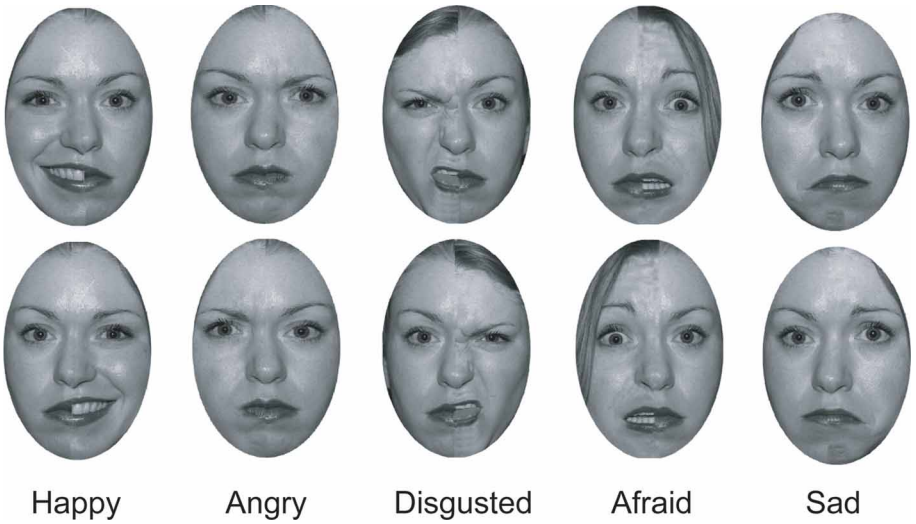


FIGURE 1 | Examples of the chimeric faces used in this study.

strongest evidence supporting this claim comes from studies using brain-damaged populations. In particular, patients with unilateral right hemisphere lesions show a decreased left hemiface bias (Kucharska-Pietura and David, 2003). In contrast, patients with unilateral left hemisphere lesions show an increased left hemiface bias (meta-analysis by Voyer et al., 2012); one interpretation is that this results from a decrease in competition from the left hemisphere. Thus, the hypothesis is that right hemisphere superiority for aspects of face (and/or emotion) processing allows better extraction of decision-critical information from chimeric faces that contain that information in the left visual field.

Although the pattern observed on the chimeric face test has often been interpreted as a stimulus-driven perceptual bias linked to hemispheric specialization, other factors have been found to modulate performance on the test. Levy et al. (1983) found stable and reliable patterns of individual differences in degree of bias on the test, even within right-handed individuals (who would be presumed to have similar patterns of hemispheric specialization), and linked these to global attentional biases. Others have suggested that the left hemiface bias may be importantly driven by well-practiced directional scanning biases, and thus not as reflective of hemispheric specialization as is typically assumed (cf. Bryden, 1966; Vaid and Singh, 1989; Heath et al., 2005). That is, the extent to which an individual has a learned tendency—for example, based on reading experience with a particular language—to scan from left to right (or vice versa) in evaluating stimuli can privilege processing in one visual field. Vaid and Singh (1989) examined this possibility by measuring performance on a happy/neutral chimeric face test using three groups whose native languages differed in their scanning patterns: Hindi readers, who scan from left to right, Arabic readers, who scan from right to left, and Urdu readers, who scan from right to left, but who also had exposure to Hindi and thus were classified as bidirectional. Consistent with a directional scanning account, this study found greater left hemiface bias in Hindi readers compared to the other two groups (Vaid and Singh, 1989).

Another study that tracked eye movements as participants viewed (male/female) chimeric face pairs also showed that decision biases were related to fixation patterns in a manner that is consistent with the directional scanning account (Butler et al., 2005). In particular, this study found that participants were more likely to show a left hemiface bias when they spent more time fixating on the left side of the chimeric face. However, a follow-up study by the same group restricted scanning time by displaying the chimeric faces for only 100 ms. They found that right-handed participants still showed a left hemiface bias, suggesting that scanning biases may not be necessary for eliciting the effect (Butler and Harvey, 2006).

Thus, it remains unclear precisely what mechanisms underlie the oft-observed left hemiface bias. In the current study, we further examine the mechanisms at work in the elicitation of this bias by examining the effect that task demands have for eye gaze patterns and choice behavior in the chimeric faces test. Prior work in the literature, as described above, has largely focused on varying the types of stimuli or the duration of stimulus presentation used in the test. No study, to our knowledge, has systematically examined how changes in task demands can affect performance on the test. Almost all studies have used relatively similar tasks in which participants' judgments about the faces are directly related to the aspects of the face that are manipulated across the two halves. For instance, studies that manipulate emotional expression ask participants to identify which of the chimeric faces look happier, sadder, angrier, etc. Studies that manipulate sex ask participants to identify which of the chimeric faces look male or female. Importantly, these manipulated characteristics are ones for which the right hemisphere might have a processing advantage (Demaree et al., 2005; Hu et al., 2013).

Critically, in this study, we compare the standard chimeric faces emotion judgment task with a task for which information

from the left hemiface would not be expected to provide decision-critical information (an "original/mirror image" judgment task, described below). We monitored eye movements to be able to look simultaneously at scanning patterns and behavioral decisions. If the tendency to look at the left hemiface is a default bias, created by reading experience or scanning patterns learned for faces, then gaze patterns should be similar in the two tasks. If, then, these patterns drive the decision bias, we should see a similar decision bias in the two tasks. This outcome would provide strong support for a scanning bias account of performance on the chimeric faces task. However, if a left hemiface bias arises because of right hemisphere specialization for extracting certain types of information, such as emotion, from faces, then we would expect a reduction or elimination of the left hemiface bias in our alternative task compared to the standard task—despite using the same subject population, the same stimuli, and the same general paradigm. Finally, if gaze patterns differ across the tasks, then this would support the view that participants may use gaze (and, by inference, attention) to strategically recruit specialized hemispheric resources to meet task demands.

METHODS

PARTICIPANTS

We recruited 66 individuals from the University of Illinois to take part in the study in exchange for monetary compensation. All participants, by self-report, were native English speakers. Eight participants were excluded, as they were classified as either left handed or ambidextrous as assessed by the Edinburgh Inventory (Oldfield, 1971). The remaining 58 participants were right-handed. Twenty-nine participants [16 females, average age = 21 (range = 18–29), handedness score = 79.3] were randomly assigned to Task 1 (emotion judgment task) and 29 participants [19 females, average age = 23 (range = 19–34), handedness score = 78.4] were assigned to Task 2 (original face judgment task).

STIMULI

We constructed chimeric faces from a set of photos of normal faces obtained from the NimStim database (Tottenham et al., 2009). We retrieved six types of emotive faces from this set: neutral, angry, happy, disgusted, sad, and fearful. Faces had been previously normed by the Tottenham et al. group to ensure that a majority of individuals correctly perceived each face as conveying a particular emotional expression.

Using Adobe Photoshop, we converted each face into gray scale and removed extra-facial details, such the head hair and ears. We created chimeric faces for each emotion category by splitting each face in half and combining the left half of a face displaying emotion with the right half of the face of the same individual displaying a neutral expression. We smoothed the area where the two halves of the faces met in order to give the appearance of a continuous face. A mirror image of each face was then produced and the faces were placed one above another, with the location of the original (e.g., emotion on the left hemiface) and the mirror-image counterbalanced. There were five categories of chimeric faces: happy-neutral, disgust-neutral, angry-neutral, sad-neutral, and fearful-neutral. In each category, there were a total of 18 unique faces (nine men, nine women). Thus, there were a total of 90 chimeric face pairs (see **Figure 1**).

PROCEDURE

Participants were tested individually in a quiet room, where they were seated 100 cm away from a 22-in. Cornerstone P1750 monitor (resolution 1024 × 768), with a refresh rate of 60 Hz. Before the experiment began, the desktop-mounted SR Research EyeLink 1000 eye tracker was calibrated for each subject with a 9-point calibration system. A chin rest was used to reduce head movements. Drift correction was done at the beginning of each trial. Recordings were monocular, taken from the right eye.

Participants that were randomly assigned to Task 1 were given a standard chimeric face test. A single trial began with the 2 s presentation of a sentence asking, "Which face looks happier/sadder/angrier/more fearful/more disgusted?" This screen was then replaced by a drift-check target. In order to advance from this target, participants had to fixate accurately on the target while pressing the advance button on a handheld controller. They were then presented with two chimeric faces. One chimeric face was presented on the top half of the screen and its mirror image was presented on the bottom half. The top/bottom location of each chimeric face (e.g., emotion on the left hemiface) was counterbalanced across participants. Participants pressed one of two buttons on a handheld controller to indicate which of the two faces was more expressive of the cued emotion; they were told to try to make their judgments in less than 10 s. In addition, they were told that the faces would be on the screen for a minimum of 10 s. This meant that if they pressed the button in less than 10 s, the faces would still remain on the screen until 10 s from the onset of the stimuli had transpired. They were then presented again with a drift check target that indicated the start of a new trial.

For Task 2, participants were given a different set of instructions. Prior to the start of the study, we showed participants pairs of chimeric faces. We told them that in order to construct the pair of chimeric faces, we first had to create an "original chimeric face" by combining two halves of photographs of the same person (e.g., left half from a photo of a person displaying happiness and right half from a photo of the same person displaying a neutral expression, or vice versa). We explained that the other chimeric face was then a mirror image of that "original chimeric face." We told participants that for each pair, they should try to determine which chimeric face was the "original" one. We expected that these instructions would motivate participants to carefully examine the faces and extract perceptual information to try to use as the basis for making these judgments; indeed, as described below, their reaction time data makes clear that they took the task seriously. However, we did not expect that participants would actually be able to accurately detect the "original chimeric face," as we don't believe there are any perceptual signatures of which side of the face the emotional (or neutral) expression was originally on. The aim was for this task to share similar task demands as the standard chimeric faces test (i.e., participants need to study the faces and make a choice decision), but under circumstances in which we can be certain that right hemisphere specializations for face processing could not provide any useful information.

Individual trials followed the same structure as in Task 1: drift check, presentation of chimeric face pairs for 10 s, and participant decision, signaled with a button press response. The same pairs of chimeric faces were presented in Task 1 and Task 2. For analysis purposes, we averaged across emotional expression to maximize our power to see task differences, since past work has shown overall left hemiface biases across types of emotional expression (Christman and Hackworth, 1993; Bourne, 2010) and since responses to different emotional expressions were not of theoretical interest here.

RESULTS

BEHAVIORAL JUDGMENTS

We analyzed the data in a logistic mixed effects model with a binomial link function, with Task (coded as "1" for Task 1 and "−1" for Task 2) as a fixed effect and participants and items (i.e., each chimeric face trial) as random effects (see **Table 1**). The dependent variable was whether the participant picked the chimeric face in which the emotional expression was presented on the left side (the left hemiface). This model revealed a main effect of Task ($z = 5.83$, $p < 0.001$): Participants were more likely to pick the left hemiface in Task 1 than in Task 2.

Next, following the analytical strategy of prior studies (Levy et al., 1983; for a review, see Voyer et al., 2012), we created a lateralization quotient (LQ) score in order to estimate the hemiface judgment bias of each participant. To calculate the LQ score, we obtained the number of times an individual selected the face in which the emotional expression was located in the right hemiface and subtracted from this value the number of times the participant selected the face in which the emotional expression was in the left hemiface. This value was then divided by the total number of trials (i.e., 90). Thus, an LQ greater than zero indicates a right hemiface bias, a score of zero indicates no bias, and a score less than zero indicates a left hemiface bias.

Consistent with previous studies, participants in Task 1 displayed a robust left hemiface bias (mean LQ score = −0.49), $t_{(28)} = -6.23$, $p < 0.001$. Strikingly, participants in Task 2 showed a much lower LQ score (mean = −0.003), $t_{(56)} = -5.75$, $p < 0.001$, which was not reliably different from zero, $t_{(28)} = -0.10$, $p = 0.92$. See **Figure 2A**. Thus, as expected, participants in Task 2 were not able to detect reliably the original chimeric face; accurate detection would have yielded a left hemiface bias, since all chimeric faces were originally constructed using the left half of emotion-conveying faces.

RESPONSE TIMES

Prior work using happy/neutral chimeric faces has shown that participants respond more quickly on trials wherein they show a left hemiface bias compared to trials wherein they show a right hemiface bias (Bourne, 2008). To test for this pattern in our data, we calculated response times from the onset of the chimeric face pairs to the participant's button press response. Trials with response times that were two standard deviations above each participant's average response time were removed, yielding an average loss of 4% of trials for Task 1 and 3% of trials for Task 2 (these trials were also removed from the LQ score and eye-movement analyses). A two-factor ANOVA with Task (Task 1, Task 2) as a between-subjects factor and Face Judgment (picked left hemiface, picked right hemiface) as a within-subjects factor revealed a main effect of Task, with Task 1 eliciting faster response times (mean = 4381 ms) than Task 2 (mean = 5415 ms), $F_{(1, 56)} = 6.71$, $p = 0.01$, and a main effect of Face Judgment, wherein trials in which participants showed a left hemiface bias (mean = 4729 ms) elicited faster response times than trials in which participants displayed a right hemiface bias (mean = 5068 ms), $F_{(1, 56)} = 14.03$, $p < 0.001$. These main effects, however, were moderated by a significant Task × Face Judgment interaction, $F_{(1, 56)} = 15.77$, $p < 0.001$.

Follow-up analyses revealed that the faster response times to left hemiface-biased trials (mean = 4032 ms) compared to right hemiface-biased trials (mean = 4730 ms) occurred only for Task 1, $t_{(28)} = 4.42$, $p < 0.001$. In Task 2, response times to left hemiface-biased trials (mean = 5425 ms) were indistinguishable from those to right hemiface-biased trials (mean = 5405 ms), $t_{(28)} = -0.23$, $p = 0.82$ (see **Figure 2B**).

GAZE PATTERNS

To examine gaze patterns, we created four regions of interest encompassing the two hemifaces of each of the two chimeric images: emotional expression on the left side, neutral expression on the right side (from one chimeric face), emotional expression on the right side, neutral expression on the left side (from the other chimeric face). We obtained the proportion of viewing time a participant spent on each of the four regions of interest by determining the duration of fixations to a given interest area and dividing that value by the combined duration of fixations for all four regions of interest. This measure was calculated for each trial, beginning from the onset of the chimeric faces and terminating when participants pressed the button to register their choice. Proportion of looks to each side of each chimeric face in each task is plotted in **Figure 3**.

In both tasks, participants gazed more overall at the emotional sides of the faces (69% in Task 1 and 57% in Task 2) than at the neutral sides of the faces (**Figure 3B**), but this bias to look at the emotional half faces was greater in Task 1 [$t_{(56)} = -5.90$, $p < 0.001$]. In Task 1, participants viewed the left halves of the faces more (53%) than the right halves of the faces, whereas in Task 2, participants were biased toward looking at the right halves of the faces (gaze proportion to left = 44%) (**Figure 3C**); this task difference in lateralized gaze preference was significant [$t_{(56)} = -2.07$, $p = 0.04$].

In addition, we examined how gaze patterns developed over time. **Figure 4** shows the proportion of viewing time directed to each region of interest across the entire 10 s that the faces were on the screen, for successive 1000 ms time bins. Viewing

Table 1 | Influence of Task on Behavioral Judgments.

	Estimate	*SE*	*z*-value	*Pr*(>|*z*|)
FIXED EFFECTS				
(Intercept)	0.71	0.12	5.67	<0.001
Task	0.70	0.12	5.83	<**0.001**

Bold values correspond to statistically significant.

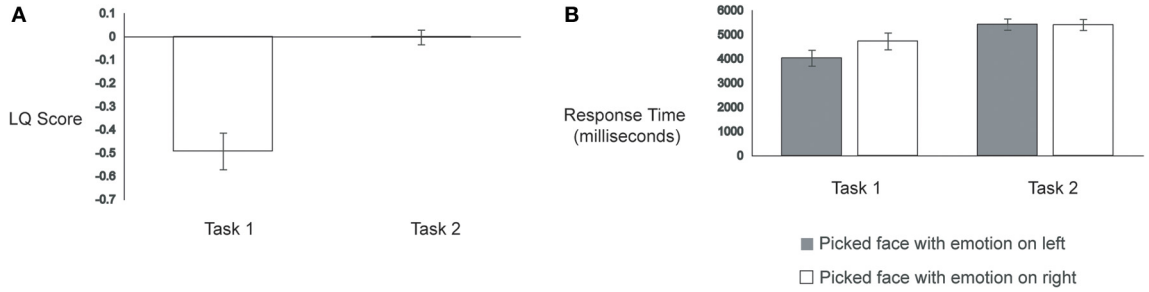


FIGURE 2 | (A) Laterality Quotient Scores and **(B)** Response Times across the two tasks.

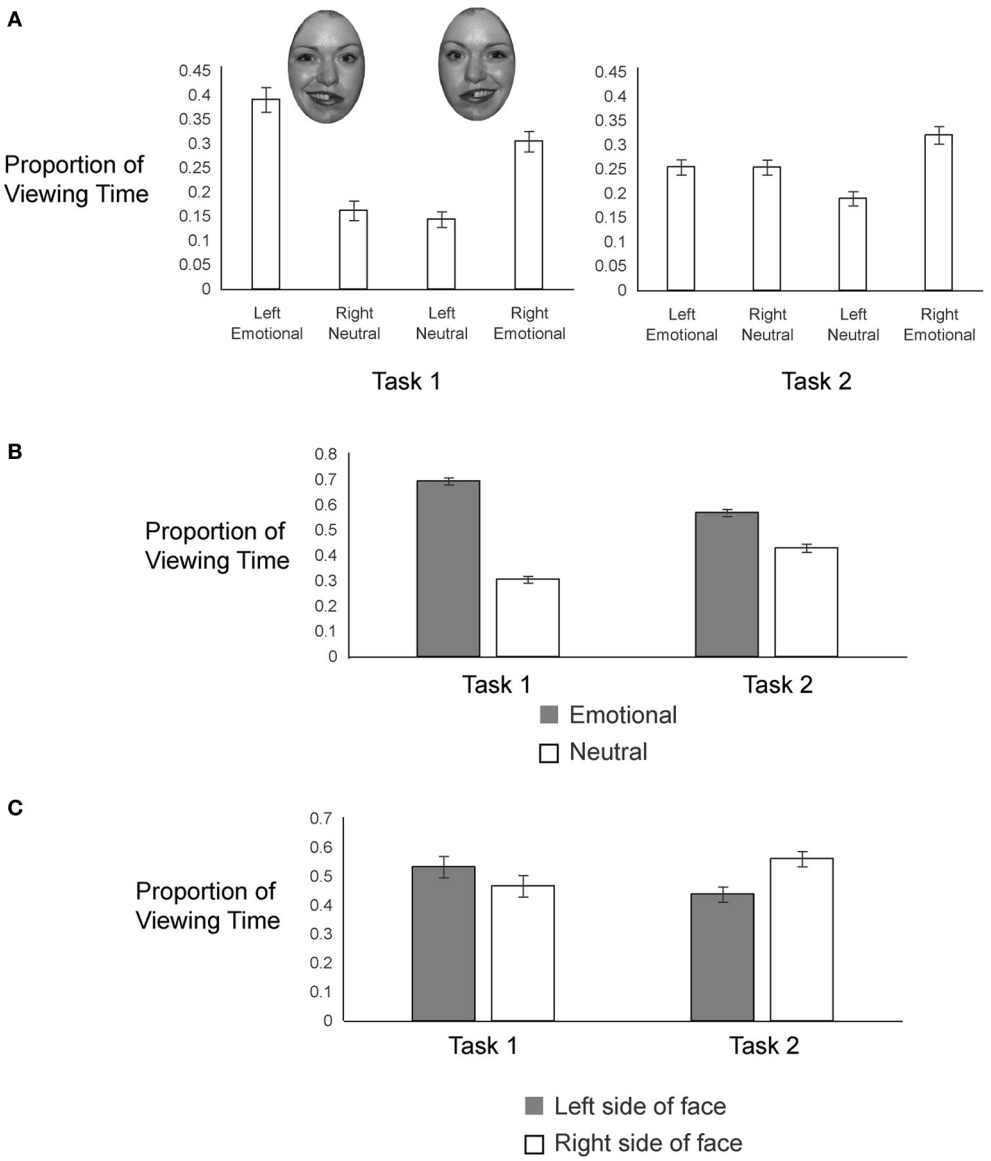


FIGURE 3 | Proportion of Viewing Time to (A) Four Regions of Interest, (B) Emotional/Neutral and (C) Left/Right Sides of the Faces Across Tasks.

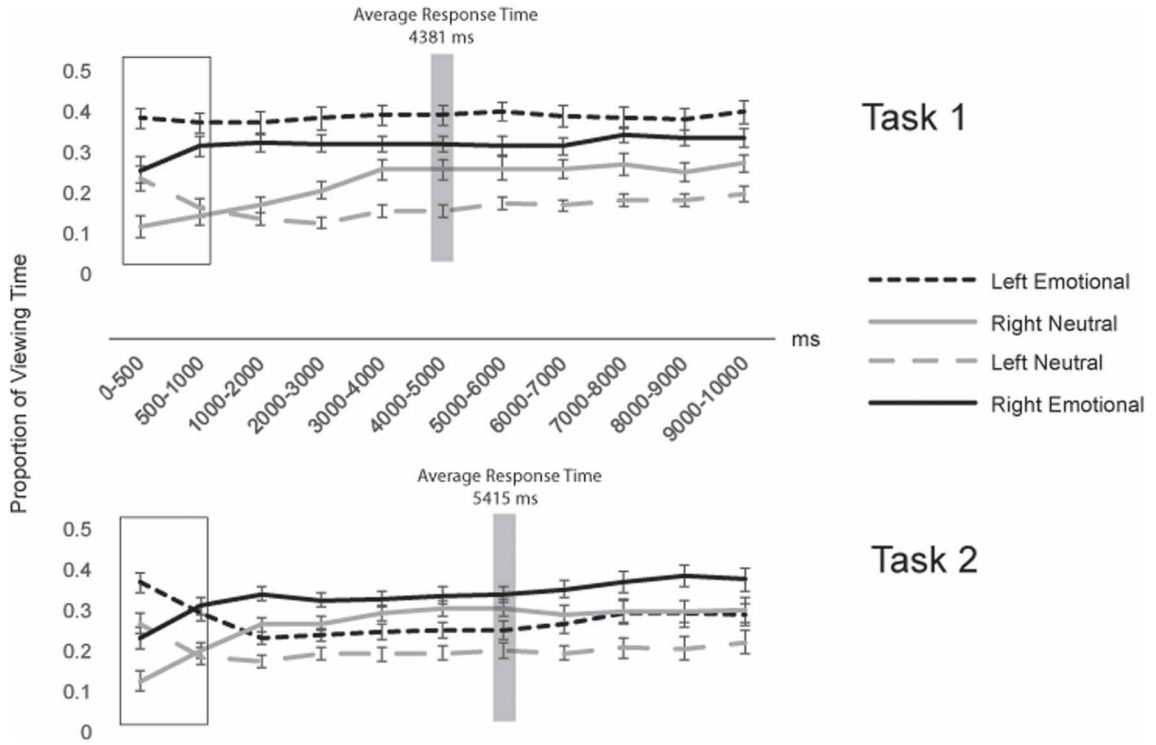


FIGURE 4 | Proportion of Viewing Time to Four Regions of Interest in 1000 ms Time Bins.

proportions were calculated separately in each bin. To capture early gaze patterns, we also split the first time bin in half, looking separately at 0–500 ms and 500–1000 ms. In the first 500 ms after stimulus onset (see box in **Figure 4**), participants in both tasks showed similar preferences to view left over right hemifaces and emotional over neutral hemifaces, resulting in the highest proportion of gaze being directed to the left emotional hemiface [38% in Task 1 and 37% in Task 2; these proportions did not differ by Task: $t_{(56)} = 0.40$, $p = 0.69$]. However, as can be seen in **Figure 4**, after the first 500 ms, gaze patterns diverged across task, such that by the 1000–2000 ms time bin, they stabilized at the pattern characterized by the overall gaze proportions (wherein Task 1 participants continued to gaze most at the left emotional hemiface, but Task 2 participants switched to gaze most at the right emotional hemiface). Importantly, this pattern was sustained up to and beyond the response times for both tasks (meaning that overall gaze patterns were not skewed by different cutoff times based on the response time difference across tasks) (see **Figure 4**).

GAZE PATTERNS AND CHOICE BEHAVIOR

Critically, the scanning bias account claims that gaze patterns prior to the behavioral decision should predict choice outcomes and should do so similarly across task. **Figure 5** shows gaze patterns as a function of task and behavioral choice. To assess how gaze patterns were related to choice behavior as a function of task, we first tested the hypothesis that a general bias to gaze at the left side of the chimeric faces predicted a left emotional hemiface bias in choice behavior. We analyzed the data in a logistic mixed effects model with a binomial link function, with Task (coded as "1" for Task 1 and "−1" for Task 2) and Left Proportion (i.e., mean-centered proportion of time spent looking on the left side of the faces) as fixed effects, and participants and items as random effects (see **Table 2**). This model revealed a main effect of Task ($z = 5.27$, $p < 0.001$): as already shown, participants were more likely to pick the left hemiface in Task 1 than in Task 2. There was also a main effect of Left Proportion ($z = 9.33$, $p < 0.001$) as participants were more likely to pick the left hemiface as they spent a greater amount of time looking at the left side of the faces. Finally, there was a significant Task × Left Proportion interaction ($z = 4.02$, $p < 0.001$): an increase in looking at the left side of the face had a greater impact on picking the left hemiface in Task 1 than in Task 2. (The same analysis done for gaze patterns between 0 and 500 ms revealed no relationship between *initial* gaze and choice behavior in either task; see Table S2 in Supplementary Materials Section).

Table 2 | Influence of Task and Gaze Patterns Directed to the Left Side on Behavioral Judgments.

	Estimate	*SE*	*z*-value	*Pr*(>|*z*|)
FIXED EFFECTS				
(Intercept)	0.67	0.12	5.71	<0.001
Task	0.61	0.12	5.27	<**0.001**
Left proportion	1.8	0.19	9.33	<**0.001**
Task * left proportion	0.77	0.19	4.02	<**0.001**

Bold values correspond to statistically significant.

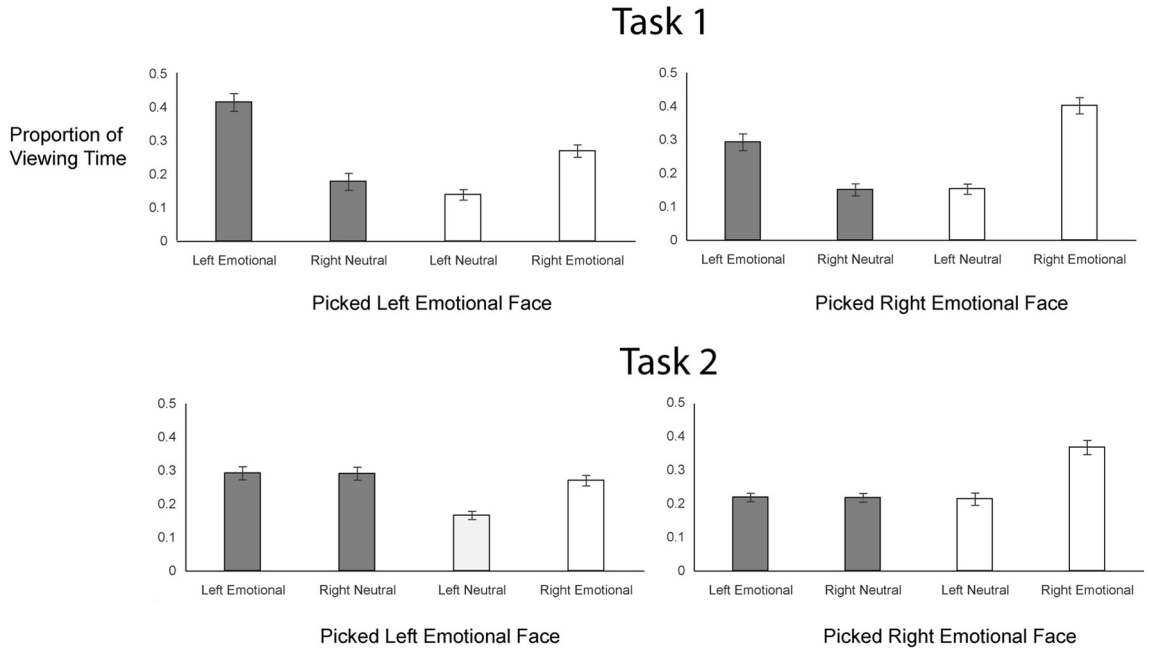


FIGURE 5 | Gaze Patterns as a Function of Task and Behavioral Choice.

We further explored this interaction by examining the relationship of gaze to each of the four interest areas on choice behavior (see Table S1 in Supplementary Materials Section). For each region, we conducted analyses using a logistic mixed effects model with a binomial link function, with Task (coded as "1" for Task 1 and "−1" for Task 2) and proportion (centered on the mean) as fixed effects, and participants and items as random effects. The main effect of Task, present in each analysis, has already been described. There were main effects of Left Emotional ($z = 15.77$, $p < 0.001$) and Right Neutral ($z = 11.88$, $p < 0.001$) proportions (i.e., interest areas that constitute the left hemiface, with emotion on the left and a neutral expression on the right). More gaze in either of these interest regions was associated with a greater likelihood of picking that left hemiface. However, choice behavior was more driven by looks to the Left Emotional hemiface in Task 1 (vs. Task 2; $z = 2.80$, $p < 0.01$), whereas it was more driven by looks to the Right Neutral hemiface in Task 2 (vs. Task 1; $z = -3.73$, $p < 0.001$). There were also main effects of Left Neutral ($z = -8.32$, $p < 0.001$) and Right Emotional ($z = -20.68$, $p < 0.001$) proportions (i.e., interest areas on the *right* hemiface), of opposite sign, as more gaze in these regions was associated with a reduced likelihood of picking the left hemiface. Task did not interact with gaze to the Right Emotional hemiface ($z = -0.20$, $p = 0.84$), but there was a significant Task × Left Neutral interaction ($z = 4.08$, $p < 0.001$), as looks to the neutral side of the face affected choice behavior more in Task 2 than Task 1.

Overall, then, as expected, participants' gaze was linked to their choice behavior, as, in both tasks, they looked more at the chimeric face that they ultimately chose. However, in Task 1, there was an overall bias to look left, associated with an increased tendency to choose the left hemiface. Participants' choices were more strongly associated with gaze to the emotional halves of the faces in Task 1 compared to Task 2 but more strongly associated with gaze to the neutral halves of the faces in Task 2 relative to Task 1.

DISCUSSION

The aim of this study was to adjudicate between two types of accounts of the widely-documented left hemiface bias in the chimeric face test. If the observed decision bias is due to scanning patterns or attentional predispositions that are applied by default, then the pattern should hold across tasks. However, to our knowledge, no one has ever previously directly compared responses to chimeric faces while manipulating task demands. Here, therefore, we used the same stimuli and asked participants to either judge which face was more emotional (i.e., one of the tasks commonly used with chimeric faces in the literature; Task 1) or to judge which face was derived from the original photographs used to create the chimeric faces (Task 2). Critically, the subject population, stimuli, and general paradigm were all identical across the two tasks; the only difference was whether the decision that participants were asked to make would likely benefit from right hemisphere specializations for extracting emotional information from faces. In addition, we used eye tracking methods to measure gaze in order to be able to look directly at scanning biases and their relationship to the decisions that participants made.

In Task 1, we replicated findings in the chimeric face literature for all of our measures. Participants showed a robust left hemiface decision bias. We also replicated previous response time results (Bourne, 2008), in that our participants were faster to respond on trials in which they picked the chimeric face with emotion on

the left than those in which they picked the face with emotion on the right. Few prior studies have measured gaze in the chimeric face task, but Butler et al. (2005) found that on trials for which participants picked the left hemiface, gaze patterns were biased, such that participants looked more at the (left) emotional side of the chosen face than the (right) emotional side of the non-chosen face. We observed an overall tendency for participants to direct gaze to the left side of the faces, consistent with the predictions of a scanning bias account, and, like Butler et al. (2005) found that an increased proportion of time spent looking at the left side of the chimeric faces was predictive of an increased left hemiface bias in choice behavior.

Of critical interest, then, was whether these same patterns would obtain when we changed the decision that participants were asked to make. In Task 2, rather than making a judgment of emotionality, participants were asked to determine which was the "original chimeric face." The directional scanning account argues that participants have a default pattern of gaze distribution over face stimuli, which may be driven in part by reading direction in the participants' native language (Vaid and Singh, 1989)—thus, predicting a left gaze bias in our English speaking population (as was obtained in Task 1). This gaze bias, in turn, is hypothesized to drive the observed asymmetry in choice behavior in the chimeric faces task. Therefore, the directional scanning account predicts that we should observe similar gaze patterns, similar choice behaviors, and similar links between gaze and choice in both tasks, given that the stimuli and participant population were the same in both. In contrast, views that link the left hemiface bias to underlying hemispheric asymmetries in the ability to derive relevant information from the stimuli should predict a diminished or absent bias in Task 2, given that the perceptual information available from the faces does not provide a basis for judging which the original face was. (Note that because all chimeric faces were actually constructed using the left half of emotion-conveying faces, a correct answer would have yielded a left hemiface bias; our design thus provides a conservative test of the scanning bias account).

We found that all measures were notably affected by task. In striking contrast to the robust left hemiface bias observed in Task 1, participants showed no response bias at all in Task 2. Thus, participants were (as expected) not able to reliably determine which face was the original one. Moreover, participants also clearly did not just adopt a strategy of using an emotionality judgment as the basis of their judgments in Task 2, as this, too, would have yielded a pattern wherein the tasks patterned similarly. Therefore, the left hemiface bias obtained only under task conditions in which hemispheric specialization for extracting information from emotional faces could provide useful decision-related information. This pattern supports the right hemisphere specialization account of the left hemiface bias and is inconsistent with the directional scanning account.

The lateralized response time bias observed in Task 1 was also absent in Task 2. Instead, participants spent more time overall rendering a decision in Task 2 than Task 1; thus, the lack of decision bias in the second task cannot be attributed to participants "giving up" and simply guessing. These longer response times likely reflect the fact that there were no immediately obvious facial characteristics that participants could use to inform their decision, whereas participants in Task 1 were explicitly cued to examine the emotive side of the face. Thus, Task 2 participants likely distributed their search patterns more thoroughly across the two hemifaces. Indeed, Task 1 participants allocated a significantly higher proportion of their gaze to the emotional sides of the chimeric faces than did Task 2 participants.

Notably, the effect of task on gaze patterns was also inconsistent with a default scanning bias account. We did find a task-independent bias to initially (within the first 500 ms—one to at most two fixations) direct gaze to the left emotional hemiface. This is the pattern described by the default scanning bias account, possibly arising from a tendency for English readers to scan initially from left to right (e.g., Vaid and Singh, 1989). However, this pattern was short-lived and uncorrelated with later choice behavior. Participants quickly (by 1000–2000 ms) adopted and sustained task-specific gaze patterns after this initial window, which then did predict choice behavior. Whereas participants in Task 1 showed a bias to direct gaze to the left, participants in Task 2 actually showed a bias to look more at the right sides of the faces. Given that the left hemisphere has been argued to be superior in extracting local facial feature information (as opposed to more holistic/global information, which has been associated with right hemisphere face processing advantages; see, e.g., Patterson and Bradshaw, 1975; Bradshaw and Sherlock, 1982; Rossion et al., 2000), this pattern may indicate that participants made greater use of local feature information in Task 2. Irrespective of source, however, the pattern is inconsistent with the claim that the participants simply had a default bias to gaze more overall at the left side of chimeric faces.

Not only did overall gaze patterns to the faces differ across task, they were also differentially linked to choice behavior in the two tasks. The tendency to look at the left side of the face, and especially the left emotional half-face, was more predictive of a left hemiface decision bias in Task 1 than in Task 2. Moreover, gaze patterns to the neutral halves of the face were differentially linked to decision biases in the two tasks: in Task 2, relative to Task 1, participants were more likely to pick a chimeric face if they gazed longer at its neutral side.

Our study, therefore, shows for the first time that changes in task demands can have a profound impact on how participants seek information from chimeric faces and on their behavioral judgments about the faces (see Stephan et al., 2003, for analogous findings on word processing). Both individually and collectively, results from our decision and eye gaze data are more consistent with a right hemispheric specialization than a directional scanning account of the left hemiface bias in the chimeric face test. This decision bias, which is associated with faster responding as well as increased gaze to the left sides of the test faces, critically depends on the availability of useful decision-related information for which the right hemisphere has been argued to have a processing advantage (Voyer et al., 2012). That is, when emotion-related (or, in other studies, gender-related; Demaree et al., 2005; Hu et al., 2013) information in the face is useful for the decision, the better extraction of that information from the left side of the face, by the right hemisphere, induces a decision bias, which has been shown to be robust even to inversion and short presentation times

(Butler and Harvey, 2005, 2006). However, when right hemisphere specialization cannot provide helpful information for the decision – as in our second task—the bias is strikingly eliminated, even with stimuli, general task demands, and participant characteristics held constant.

Finally, the observation that not only decision biases, but also gaze patterns and their relationship to participants' decisions changed with task demands, suggests that gaze, and by extension attention, may facilitate the flexible recruitment of specialized hemispheric resources. Levy and Trevarthen (1976) described what they called hemispheric "metacontrol" or the mechanisms governing which hemisphere will attempt to control information processing operations for a given task. In the chimeric faces task, Urgesi et al. (2005) have dissociated metacontrol (which hemisphere influences the response) from hemispheric specialization (right hemisphere advantages for face processing, which were seen independently of metacontrol). The present results indicate that under conditions in which the right hemisphere has an advantage for extracting decision-relevant information from a face, participants direct more gaze toward the left halves of faces. Moreover, the extent to which gaze to the left emotional hemiface predicts left hemiface bias differs across tasks and is stronger under a condition in which emotion is cued as a decision-relevant information. This pattern is consistent with Adam and Güntürkün's (2009) proposal that metacontrol might arise via a winner-takes-all type of mechanism, wherein a small initial processing advantage for one hemisphere, combined with commissural inhibition, yields unilateral dominance over the course of processing. Our data extend this proposal by suggesting a role for gaze and attention in mediating the development of this shift. Indeed, Stephan et al. (2003) found that task-related changes in processing asymmetry are associated with a corresponding change in the lateralization of control networks, including the anterior cingulated cortex, which has been linked to both attention (e.g., Weissman et al., 2004) and eye control (e.g., Paus et al., 1993). The present results suggest that gaze patterns are adapted to task demands in a manner that can facilitate hemispheric metacontrol and allow the recruitment of task-relevant asymmetric processing resources.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.00229/abstract

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In (or outside of) your neck of the woods: laterality in spatial body representation

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Beside language, space is to date the most widely recognized lateralized systems. For example, it has been shown that even mental representations of space and the spatial representation of abstract concepts display lateralized characteristics. For the most part, this body of literature describes space as distal or something outside of the observer or actor. What has been strangely absent in the literature on the whole and specifically in the spatial literature until recently is the most proximal space imaginable – the body. In this review, we will summarize three strands of literature showing laterality in body representations. First, evidence of hemispheric asymmetries in body space in health and, second in body space in disease will be examined. Third, studies pointing to differential contributions of the right and left hemisphere to illusory body (space) will be summarized. Together these studies show hemispheric asymmetries to be evident in body representations at the level of simple somatosensory and proprioceptive representations. We propose a novel working hypothesis, whereby neural systems dedicated to processing action-oriented information about one's own body space may ontogenetically serve as a template for the perception of the external world.

Keywords: left–right handedness, lateralization, personal space, body representation, somatosensation

INTRODUCTION

Whether we navigate through an unknown environment, cross a busy street or give somebody directions by pointing to a location, for most of us, parts of our right hemisphere will be active (e.g., Kinsbourne and Bemporad, 1984; Corbetta and Shulman, 2002; Craig, 2002; Vogel et al., 2003). Of course this does not mean that the left hemisphere will be silent. Rather, in comparison to tasks which involve more left-hemispheric functions such as language (Grunwald et al., 2001), the spatial processing required during the above examples recruits predominantly right lateralized circuits (Stephan et al., 2007). Besides language, spatial processing is the most widely recognized and best studied lateralized system in the human brain (Gotts et al., 2013).

Lateralization for spatial processing is evident on three levels. First, a behavioral index is provided by the level of success with which spatial tasks are performed by people presumed to be lateralized to a greater degree (i.e., right-handers) compared to people with more bilateral functioning (i.e., mixed-handers and some left-handers; Knecht et al., 2000; Szaflarski et al., 2002). While handedness only constitutes an imperfect proxy for laterality, the general finding is that spatial ability declines with increasing dextrality (Annett, 2002; cf. Gotts et al., 2013). For example, neurologically normal right-handers, but not mixed and left-handers, typically misbisect a line to the left of true center (Jewell and McCourt, 2000; cf. Scarisbrick et al., 1987) – a small spatial bias termed "pseudoneglect" (Bowers and Heilman, 1980). Second, cerebral functioning studies provide evidence of right hemispheric dominance for the processing of spatial tasks (for a meta-analysis, see Vogel et al., 2003) and patients suffering from right hemispheric damage exhibit marked spatial deficits (Kerkhoff, 2001). Finally, a third level of laterality description is that of macro- and microstructural differences between the right and left hemisphere generally (e.g., Thiebaut de Schotten et al., 2011), as well as between the corpus callosum of individuals lateralized to a greater, and those to a lesser degree (e.g., Witelson, 1985; Habib et al., 1991; Jäncke and Steinmetz, 2003; Westerhausen et al., 2004).

Both behavioral and functional studies are most often concerned with visuospatial processing of external space. That is, by far the greatest amount of knowledge on the laterality of spatial processes concerns the visual modality and the perception of the region of space that is within one's reach (i.e., peripersonal space) and the region of space outside of one's reach (i.e., extrapersonal space). However, it is also known that lateralization of spatial processing extends to other modalities and even to the mental representation of space and abstract concepts like numbers. Similar to pseudoneglect for the visual variant of the line bisection task, for example, haptic bisection also results in a systematic bias in right-handers (Sampaio and Chokron, 1992; Brodie and Dunn, 2005; Hach and Schütz-Bosbach, 2012) and mental representations of space are frequently affected by a hemispatial bias in patients suffering from visuospatial neglect (Bisiach and Luzzatti, 1978; Bartolomeo et al., 1994; Landi et al., 1997). As a result of the focus on the visual modality, discussions and examinations of representations of our own body, dominated by the tactile and proprioceptive sense, are almost completely absent from the spatial literature. Yet, our own body represents a crucial spatial compartment and, in extension to peri- and extrapersonal space, may be

conceptualized as a third region of space. It is this third region of space that forms the main focus of the current review.

BODY SPACE

Body space is simply defined as the space that our own body inhabits. For the purpose of this review and the working hypothesis we propose as part of the conclusion to this review, body space constitutes a superordinate concept including at least two different body representations that have been proposed to exist in the past. Specifically, the body schema, or a low-level egocentric, action-oriented representation of one's own body in terms of tactile and proprioceptive information (for various definitions of this concept, see Head and Holmes, 1912; Haggard and Wolpert, 2005; Holmes and Spence, 2006), forms an important part of body space. Similarly, however, the body image may be seen as a part of body space. Body image, here, refers to an abstract representation of one's own body that includes a conscious and emotional evaluation of the visual characteristics of the body (Paillard, 1999; Gallagher, 2005). This representation is thought to be coherent across space and time and, importantly, distinct from the body schema (Paillard, 1999; Gallagher, 2005; Schwoebel and Coslett, 2005; Dijkerman and De Haan, 2007). In addition to the body schema and the body image, other forms of body representations, such as left-lateralized linguistically mediated representations, have importantly been proposed to exist (e.g., Coslett et al., 2002; Schwoebel and Coslett, 2005; Dijkerman and De Haan, 2007), but are considered distinct from the current conceptualization of body space.

Body space, including the different forms of representations mentioned above, distinguishes itself from peri- and extrapersonal space with regard to two aspects. First, representations of our own body are always immediate, inescapable and tied to the first person perspective. That is, there is no possibility of separating oneself from body space – an observation recorded as early as the late 1800s by James (1890). Second, interoception, or the "sense of the physiological or homeostatic condition" of our own body (Berlucchi and Aglioti, 2010, p. 31), provides a unique and private source of information about the state of this space, that is lacking for the perception of peri- and extrapersonal space. There is extensive evidence showing interactions between body space, peripersonal and extrapersonal space. Specifically it has been shown that the border between what is perceived as within or outside of one's reach, or neck of the woods, is heavily dependent on the representation of body space (e.g., Pavani and Castiello, 2004; Coello et al., 2008). However, it remains an empirical question whether the aforementioned special characteristics of body space mean that this third region of space can or cannot be subsumed under the heading of spatial perception. In other words, it is unclear whether general rules of spatial perception, specifically those applying to action-oriented egocentric representations of space, also apply to the perception of body space.

One first, and admittedly crude, level of examining this is laterality. Findings showing that body space perception, like that of external space, is largely right-lateralized could be first evidence that, although special with regard to the two points mentioned above, body space can be subsumed under the supramodal heading of spatial perception. In the following, we will summarize the state of evidence of hemispheric asymmetries in body space representation from three perspectives. First, body space in health and second, body space in disease will be examined. Specifically, body space asymmetries in right-handers and two descriptive examples of disorders of body space, namely somatic neglect and eating disorders, will illustrate the crucial contribution of the right hemisphere to these representations. Third, studies pointing to differential contributions of the right hemisphere to illusory body space, using the example of the rubber hand illusion (RHI), will be summarized. Examples from all three levels of description of laterality, namely behavioral, functional, and structural studies will be taken into account.

BODY SPACE IN HEALTH

Returning to the example of everyday spatial processing given at the outset of this review, the area of navigation has provided some of the best-known literature on spatial processing (e.g., Craig, 2002). Navigational experts like London taxi and bus drivers are widely known to show greater posterior hippocampal volume bilaterally. Right hippocampal volume, in particular, correlates with the number of years of navigational expertise (Wagner et al., 2003; Nico et al., 2010). It is also known that bilateral hippocampal lesions lead to a loss of some of the flexibility with which the navigational expertise acquired prior to injury can be applied (Guardia et al., 2013). Most of these well-known examples focus on navigational skills which require an abstract, view-independent or allocentric representation of external space.

A related line of research examines spatial processing from the egocentric perspective, and has received comparatively little attention. Specifically, studies examining navigational behavior in relation to handedness have shown that healthy right-handers exhibit a behavior similar to stroke victims suffering from neglect. While it is common for right parietal lobe stroke victims to collide with objects to their left when navigating through tight spaces (Tsakiris et al., 2007a; Bekrater-Bodmann et al., 2012), Turnball and McGeorge (1998) presented observational data showing the opposite bias in healthy right-handers. That is, right-handers were found to be more likely to collide with objects on their right. A series of more recent studies has confirmed and extended this finding to show that the extent to which right-handers display a leftward bias on the classical line bisection task is significantly associated with the number of rightward collisions (Nicholls et al., 2007, 2008b) and that navigational displays viewed in the upper, but not the lower, visual field result in a greater chance of rightward collisions (Thomas et al., 2009).

While the authors of the above studies attributed the navigational bias in right-handers only to a biased perception of the display provided (in most studies this is a narrow doorway or corridor), one additional factor that may act together with a biased perception of the peri- and extrapersonal space as well as a host of other factors (e.g., differential movements of the right and left upper limbs, see Nicholls et al., 2007, 2008b) to produce lateralized collisions has been left largely unexplored. It could be argued that just as much as the perception of the external environment, an accurate perception of where in space one's own body is and how wide/narrow it is in different places is required for this task.

Thus, an additional contributing factor to right-handers' bumping behavior could be a less precise perception of their own body. Due, in part, to the scarcity of validated tests for the assessment of representations of body space, this question has not been addressed in depth until recently.

A few existing examinations of representations of body space employ a task parallel to the traditional line bisection task. Here participants are required to point to their body midline or to a location ahead of them which corresponds with their body midline (also termed subjective sagittal middle). Three studies examined handedness differences in this task and report findings broadly congruent with pseudoneglect. Spidalieri and Sgolastra (1997) and Chokron et al. (2004) reported that right-handed participants pointed significantly to the left of their midsagittal plane when using their left hand, while another study found a significant bias to the left for both right- and left-handers (Colliot et al., 2002). Using this task it is not possible, however, to distinguish between a bias affecting pointing actions and a spatial bias which affects the representation of one's own body. Further, a midsagittal pointing task could be argued to draw less on a spatial representation of the body as a whole.

A different task which is superior in that it requires many body surface locations to be transformed into locations in external space (cf. Yamamoto and Kitazawa, 2001) is the Fluff Test. Here, a number of cotton balls are attached to the blindfolded participant's clothes. Subsequently, the participant is required to recover these. Using this task, first evidence of a body space bias in neurologically healthy right-handers beyond a pointing bias such as that documented using the midsagittal pointing task was found by Cocchini et al. (2001). For their validation of the Fluff Test, which was aimed at assessing somatic neglect in stroke patients, the authors also examined the performance of a group of control participants. A trend toward handedness differences was found with some left-handers outperforming right-handers.

A more recent study conducted at our lab improved the sensitivity of the Fluff Test by increasing the number of items to be recovered from the body surface (Hach and Schütz-Bosbach, 2010). By using a tight-fitting full body suit equipped with the stimuli that were to be recovered, some limitations such as the potential of tactile feedback during the placement of the cotton balls on the clothing of the participant were also removed. We confirmed the original trend and showed that right-handers generally showed less exploration of their body surface in comparison to left-handers. In line with studies reporting handedness differences for cognitive domains as diverse as attention, decision making or memory (e.g., Annett, 2002; Propper et al., 2005; Christman et al., 2007b), we interpreted this as an indication of right-handers having less access to right hemisphere processing. Functional access in this case refers to the recruitment of specialized neural structures for performance on a task that is high on the demands of this particular ability and "better functional access" results from greater neural interconnectivity (higher number of white matter tracts/synapses; He et al., 2007). Further, when biomechanical constraints were taken into account, a particular advantage for the right (or disadvantage for the left) side of the body seemed to be present for this group of participants.

Moreover, we also introduced a quantitative measure of the putative body space bias, the Body Outline Pointing Task (Hach and Schütz-Bosbach, 2010). This measure requires participants to point to the widest and narrowest part of their hidden body on their right and their left side in three locations. A comparison of participants' pointing scores for the left and right hemispace can be used to determine a side bias. In addition, a more precise measure of participants' ability to judge the *actual* spatial dimensions of their own body is possible by utilizing measurements taken from a standardized photograph of the participant. We found right-handers to show a spatial asymmetry with respect to the distance from the midsagittal plane in two out of the three locations when comparing left- and rightward pointing movements. Their estimate of the narrowest part of their right waist as well as of the widest part of their right hip was found to be more distant from the midsagittal plane and importantly closer to their actual body boundary compared to their estimate of the left waist and hip. Significant correlations between performance on this task and individual participants' laterality quotients further showed that performance decreased with increasing dextrality.

Other work showing evidence consistent with the conclusion that right-handers represent body space less precisely than left-handers includes that of Linkenauger et al. (2009). According to their findings, right-handers significantly overestimate the length of their right arm and the size of their right hand while left-handers show no such asymmetry. There is also some evidence of greater areas of somatosensory cortex devoted to the representation of the right hand in right-handers (Sörös et al., 1999). However, other studies have failed to replicate this finding (e.g., White et al., 1997; Jung et al., 2003). Nevertheless, there is the possibility that in addition to less access to, or an overall less precise, structural representation of the body in right-handers, there may be more "hardware" devoted to the representation of the dominant side of the body causing right-handers to show some asymmetry in judging spatial properties of their own body.

To summarize the literature reviewed thus far, there is first evidence of laterality effects in the spatial representation of the body of healthy individuals. Right-handers show a bias not only with respect to judging external space but also with judging the spatial characteristics of their own body (see **Figure 1B**), and this bias is absent in the performance of left-handers. Moreover, the reported effects relate to an action-oriented moment-to-moment representation of the spatial properties of our body akin to the body schema, which may be supported by automatic sensorimotor loops independent of explicit awareness (Paillard et al., 1983; Paillard, 1999; Rossetti et al., 2005; Gallace and Spence, 2008).

BODY SPACE IN DISEASE

One condition previously mentioned in relation to the mental representation of space and the spatial representation of abstract concepts as well as in relation to dysfunctional navigation behavior is that of hemineglect. Hemineglect probably constitutes the most striking disorder which can result from disruptive perfusion from the middle cerebral artery. Most commonly, hemineglect results from right hemispheric infarcts (Bisiach and Vallar, 2000;

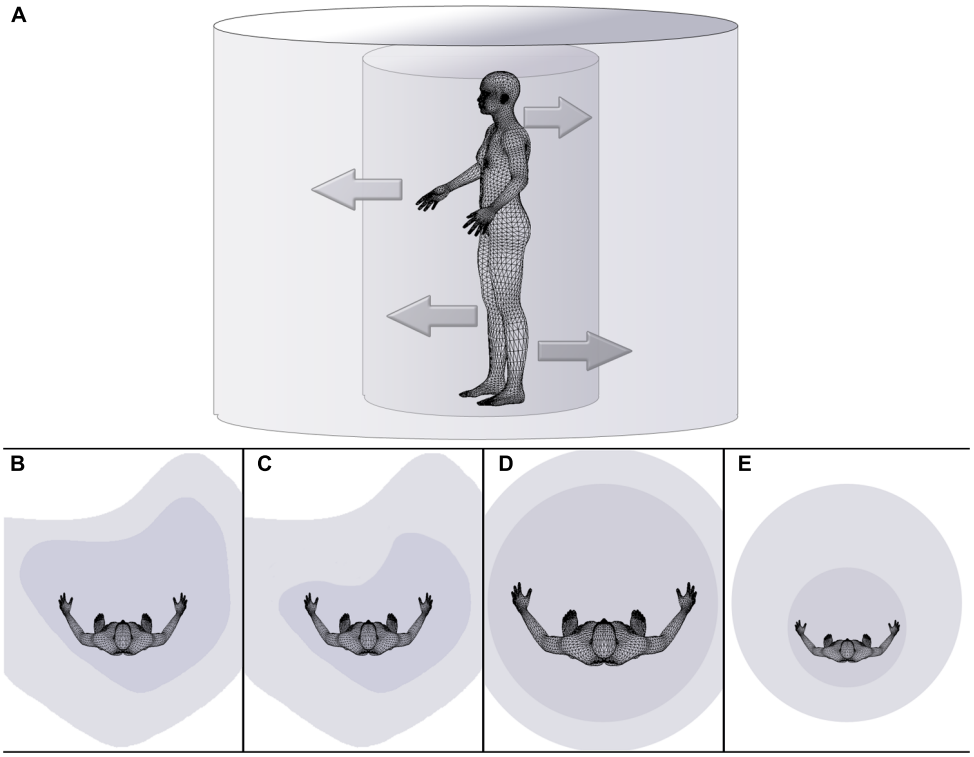


FIGURE 1 | Schematic drawing illustrating the dependency of the extent of peripersonal and extrapersonal space on body space in health (A,B), disease (C,D), and during a body illusion (E). (A) The inner cylinder represents peripersonal space, while the external cylinder symbolically represents extrapersonal space. The inner arrows symbolize the dependency of the extent or size of peripersonal space (i.e., the internal cylinder) on the state of body (space), while outer arrows pointing from the inner to the outer cylinder symbolize the dependency of the extent or size of extrapersonal space on the state/size of peripersonal space. Distorted space perception is illustrated for healthy right-handers **(B)**, individuals affected by hemispatial neglect **(C)**, individuals effected by eating disorders on the example of anorexia nervosa **(D)**, and individuals experiencing a small body illusion (e.g., van der Hoort et al., 2011; Banakou et al., 2013) **(E)**.

Kerkhoff, 2001), although sporadic reports of left hemispheric origin also exist (e.g., Peru and Pinna, 1997). In the absence of sensory deficits, individuals with hemineglect display a decreased propensity to recognize and act on objects located contralesionally, although implicit recognition may be preserved (Brozzoli et al., 2006). While most studies concentrate on peri- and extrapersonal space deficits, deficits in the representation of the stroke patient's own body have also been reported (Bisiach et al., 1986; Committeri et al., 2007). In other words, in addition to a deficit in perceiving extrapersonal space (see **Figure 1C**), a diminished perception of the contralesional body half, or somatic neglect, is present in some cases. First reports of disturbances of this nature date back as far as the early 1900s (Head and Holmes, 1912; Pick, 1922) but few in-depth reports of this condition have emerged since.

Somatic neglect describes a complete disregard of the contralesional side of the patient's body. For example, these patients may comb their hair, shave or dress only the non-affected right side of their body (e.g., Bisiach et al., 1986). Measures aimed at detecting and quantifying these deficits are structured in a similar way in that they require the patients to perform reaching movements for their contralesional extremity or the contralesional side of their body (Reaching Task: Bisiach et al., 1986; Fluff Test: Cocchini et al., 2001; Comb, Razor and Glasses Test: Zoccolotti and Judica, 1991). When asked to complete the subjective midsagittal task described above, a lateral translation to the right is frequently observed (Richard et al., 2000, 2004a,b; Saj et al., 2006). Overall, however, there has been a paucity of sensitive tasks, and existing measures are mostly not part of routine assessment following admission to hospital with cerebral infarction. For this reason, it is difficult to draw conclusions about important questions such as the frequency with which somatic neglect occurs, the extent to which a decrease in the awareness of one's own body space is typically shown, the duration of this deficit and what impact it has on the patient's daily life.

There is also inconclusive literature regarding the association between somatic or personal neglect and extrapersonal hemineglect. That is, a decrease in the awareness of one's own contralesional hemibody may or may not be associated with neglect of peripersonal and extrapersonal space (Bisiach et al., 1986; Zoccolotti and Judica, 1991; Beschin and Robertson, 1997; Ortigue et al., 2006; Committeri et al., 2007). On the whole it appears that more instances of isolated extrapersonal neglect than instances of pure somatic neglect have been found, however. The contradictory state of the literature may, in part, result from the use of different measures of somatic neglect in different studies

(Guariglia and Antonucci, 1992), the different levels of severity of deficit examined or the varying temporal intervals between infarct and assessment.

Similarly, to date only two studies have examined the effectiveness of prism adaptation on the extent to which somatic neglect signs are shown, and their results contradict each other. As part of this intervention, patients wear prism glasses, which induce an optical shift. Following an initial adaptation phase during which pointing movements are performed in a spatially shifted manner, the oculomotor system resets itself and the patient's movements will be adjusted for the optical shift (Luaute et al., 2006a,b). Short-term use of prisms has been found beneficial in the treatment of hemineglect, in the amelioration of representational neglect (e.g., spatial representation of time; Magnani et al., 2011) as well as spatial deficits shown in other modalities including audition (Buxbaum et al., 2004; Hamilton et al., 2008; Jacquin-Curtois et al., 2010). In a detailed study of the effect of prism adaptation on different aspects of somatic neglect, an improvement of tactile performance was found, which resulted in a significant decline in somatic neglect symptoms on clinical assessment (Serino et al., 2007). This contrasted with no beneficial effect for proprioceptive and motor symptoms for the same patients. A smaller, more recent study failed to show any long-term effect of prism adaptation on personal space representations (Rusconi and Carelli, 2012), although follow-up reports are necessary, as the study sample of this preliminary report only comprised three patients.

Turning from the behavioral level of description to the functional level, it was noted earlier that traditionally right middle cerebral artery infarcts have been associated with hemispatial deficits. Crucially, areas in the vascular territory of the right middle cerebral artery not only support processing of peri- and extrapersonal space (Pouget and Driver, 2000; Driver and Vuilleumier, 2001; Husain and Nachev, 2006), but also the representation of personal or body space (Kinsbourne and Bemporad, 1984; Colby and Duhamel, 1996; Graziano and Cooke, 2006). On measures of somatic neglect, cortical areas as disparate as the supramarginal and post-central gyrus as well as the medial white matter (Committeri et al., 2007) and the superior temporal gyrus (Karnath et al., 2004, 2011) may be involved. In addition, personal neglect may be the result of a functional disconnection between primary regions for coding proprioceptive and somatosensory input and regions coding a more abstract spatial representation of the body (Committeri et al., 2007).

In line with some of these findings, studies that investigate patients with conditions related to somatic neglect, such as autotopagnosia, suggest a key role of the right inferior parietal lobe (e.g., Ogden, 1985; Sirigu et al., 1991; Buxbaum and Coslett, 2001). Autotopagnosic patients display a deficit in maintaining spatial relationships of body parts and make mislocalization errors when asked to point to specific body parts. Hemianesthesia has also been reported to occur more frequently following right brain damage (Sterzi et al., 1993) and anosognosia, a lack of conscious awareness of a deficit often concomitant to hemineglect, is associated with right parieto-temporal lesions (Orfei et al., 2007). Finally, somatoparaphrenia, a condition where ownership of individual limbs is consistently ascribed to somebody else, is typically associated with right hemispheric damage (Bottini et al., 2002; Vallar and Ronchi, 2009).

These latter studies are important in providing robust evidence regarding well-circumscribed areas of the brain, which support representations of one's own body. Valuable insight into more theoretical questions can also be gained from experimental studies of individual patients suffering from any of these conditions. A nice example of this is a study by Fotopoulou et al. (2011) which examined the performance of two somatoparaphrenic patients before and after mirror box therapy. Therapy was successful in transiently reinstating limb ownership when a third person perspective was experimentally induced, but this was not accompanied by an improvement of somatoparaphrenia symptoms beyond the experimental session. Both patients showed extensive damage encompassing most of the right parietal and temporal lobes, which does not allow any precise conclusions about the exact networks supporting limb ownership. However, the results crucially suggest that body ownership is largely driven by an egocentric representation of the body (Blanke et al., 2004; Tsakiris et al., 2007b; Petkova et al., 2011).

Relatedly, it has been proposed that allocentric, or viewer-invariant, neglect always occurs concomitant to egocentric neglect (Grunwald et al., 2001; Rorden et al., 2012). That is, aside from the question of which regions of space are affected separately or in combination by hemineglect (i.e., somatic neglect with or without extrapersonal neglect), patients showing deficits in recognizing target objects on the left side of the page (egocentric neglect) often also show deficits in recognizing individual targets if the defining feature is on the left side of the target object, regardless of the location in which it is presented in egocentric coordinates (allocentric or object-based neglect). Although this may depend on the exact nature of the search task and the characteristics of the stimuli (see Gainotti and Ciaraffa, 2013 for a dissociative account of ego- and allocentric neglect), it may be deduced that the ability to recognize and process external objects as a whole from one's own perspective contributes to a representation of the same object in a manner that is separate from that perspective. Similarly, the representation of our own body from our perspective is the most immediate and private representation of space, and this representation may enable us to not only construct an allocentric model of our own body, but also a model of space outside of our own body (see **Figure 1A**). As shown above, higher-order deficits, such as extrapersonal neglect or somatoparaphrenia, can frequently result from a difficulty in synthesizing the lower-order moment-to-moment representation of one's own body with the representation of external spatial cues as well as the visual/external cues about the spatial properties of one's own body.

A second example of a well-known set of disorders which affect the spatial representation of one's own body is that of eating disorders. In contrast to somatic neglect and some of the related syndromes described above, it is usually assumed that, in eating disorders, the body image is affected (e.g., Kinsbourne and Bemporad, 1984). As a result of a negative evaluation of their own body, individuals with eating disorders go to extreme lengths to alter the appearance of their body. Disturbances of the body image are most frequently assessed using questionnaires and tests that tap into the conscious and emotional evaluation of body space. For example,

Hennighausen and Remschmidt's (1999) Computer Body Image Test contains partly distorted individual body outlines, generated by the tracing of a photograph of the patient's body. The patient is then asked to adjust the body outline according to the estimated true size of his or her body outline. This test can be regarded as an explicit measure of how body space is represented in the sense that it requires a memory-based recall of the spatial dimensions of one's own body that is independent of direct primary somatosensory inputs due to movement.

Nonetheless, the body image also constitutes a kind of structural and geometric representation of the body. That is, the body image is principally dependent on and influenced by primary somatosensory inputs (cf. e.g., Lackner, 1988; Gandevia and Phegan, 1999; Schütz-Bosbach et al., 2009a). This is especially true during development. More recent investigations of participants with a history of eating disorders have begun to acknowledge this interdependency and include tests of primary sensory and motor representations of the body. As a result, it is now known that individuals with anorexia nervosa perform more poorly on tests requiring the integration of primary sensory input with external spatial reference frames. Marked deficits have been reported for the haptic reproduction of random shapes (Grunwald et al., 2001) and for the alignment of the subjective vertical with the external reference frame (Guardia et al., 2013), for instance.

Individuals with anorexia nervosa also show deficits in tasks assessing their ability to perform motor imagery. In a study by Guardia et al. (2012), anorexia nervosa patients and a group of control participants were required to perform a task similar to the navigation and handedness studies summarized above. A navigational display containing a doorway of varying size was presented. Instead of navigating through the doorway, participants remained at a fixed distance to the display and had to judge whether or not they could fit through without turning sideways (first-person condition). In an additional condition, the same judgment had to be made about the experimenter standing in the same position as the participant for the first-person judgment (third-person condition). There was a significant difference between first- and third-person perspectives only for participants with a history of anorexia nervosa. These patients overestimated the dimensions of their own, but not the experimenter's body, relative to the doorway. Importantly, this difference was not due to decreased perceptual discriminability in the patient group.

These findings are consistent with a number of other reports showing a lesser ability of anorexic participants to directly, or indirectly, estimate their body boundaries (see **Figure 1D**). For example, Christman et al. (2007a; see also Niebauer et al., 2002) found a significant correlation between the absolute value of handedness and the discrepancy between actual and estimated body mass index (BMI): the greater the degree of right-handedness, the greater the discrepancy between the true and estimated BMI. The authors suggested that greater lateralization in right-handers leads to diminished access to right hemisphere processing and, as a result, to an impoverished representation of the body. Similarly, in an indirect measure of body boundaries, Nico et al. (2010) found anorexic patients to be less accurate in their estimation of the width of their left upper body. Crucially, performance of anorexia nervosa patients was comparable to that of a group of participants with a history of right parietal lesions.

Finally, a few studies have investigated body representation in individuals with eating disorders with the use of the RHI paradigm. A summary of the experimental procedure typically employed for this illusion will be given below. For the moment, it is sufficient to say that the illusion critically involves a comparison of the experimentally manipulated tactile and visual information with the proprioceptive information about the position of one's own hand. Since the representation of the hand is not usually a focus of body concerns or emotional biases, this illusion is arguably better-suited to the study of body awareness in individuals with eating disorders compared to any of the paradigms mentioned above (Schütz-Bosbach et al., 2009b). Eshkevari et al. (2012) and, prior to that, Mussap and Salton (2006) found a relationship between the extent of psychopathology and the strength of the illusion. Specifically for the former, nearly a quarter of the variance in the strength with which the illusion was felt was explained by interoceptive deficits and self-objectification. Participants with increased scores on interoceptive items (e.g., "I don't know what is going on inside me.") of the Eating Disorder Inventory and increased scores on a self-report assessment of self-objectification showed a greater behavioral effect of the illusion (i.e., greater proprioceptive drift). In sum, studies examining the susceptibility of individuals to the RHI are consistent with the theory of right hemispheric dysregulation and resulting body spatial deficits in individuals with eating disorders.

ILLUSORY BODY SPACE

The use of illusory paradigms to study body awareness has a long tradition, particularly in the literature examining neurologically healthy individuals. These studies typically create a mismatch or dissonance between the sensory modalities, and capture participants' responses both on a qualitative or subjective level (with the use of questionnaires) and a quantitative level (an objectively measurable effect such as the displacement of a body part). Somatosensory illusions provide an excellent demonstration of the malleability of the boundary between external and body space. In other words, what is experienced as embodied space at one moment becomes disembodied as a result of the illusion being induced a moment later (see also Holmes and Spence, 2006 for the concept of excorporation). And the reverse is true as well, with external space transforming into embodied space (i.e., incorporation).

The RHI constitutes one of the most widely used examples of perceptual illusions employed to study aspects of body representation, body awareness, and body ownership. The typical set-up includes a screen which conceals one of the participant's hands and forearm from their view, a prosthetic (rubber) hand, which is placed in an anatomically plausible position to the participant's body (cf. Armel and Ramachandran, 2003; Tsakiris and Haggard, 2005) and a set of stroking devices. In a block-wise fashion, the participant's concealed hand and the prosthetic hand are stroked in a synchronous or asynchronous manner. While synchronous stroking induces a displacement of the tactile stimulation toward

the location of the prosthetic hand (i.e., the illusion of the tactile sensation originating from the seen rather than the felt position), asynchronous stroking does not usually produce such a displacement. Both horizontal and vertical experimental set-ups have been used to successfully evoke displacement in the left–right and up–down direction, respectively (Haggard and Jundi, 2009; Bekrater-Bodmann et al., 2012). Participants' responses are measured with regard to the phenomenological experience of ownership over the prosthetic hand (Longo et al., 2008), and with respect to sensory aspects of the illusion such as the degree of displacement (also commonly termed proprioceptive drift).

Perhaps unsurprisingly given the spatial nature of the illusion and the involvement of representations of the body, it has repeatedly been shown that extensive right hemispheric networks appear to support the illusion. Converging evidence from functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and lesion studies point toward the temporo-parietal junction (Tsakiris et al., 2008), inferior parietal lobule (Kammers et al., 2008), posterior insula (Tsakiris et al., 2007a), and ventral premotor and cerebellar areas (Ehrsson et al., 2004, 2005; Zeller et al., 2011) as contributing to some aspects of the illusion.

While it may be said that due to their exclusive focus on representations of the hand, RHI findings are limited in the conclusions that can be drawn about representations of the body as a whole, other studies have successfully created the illusion of incorporating a foreign body using a similar tactile stimulation procedure (Lenggenhager et al., 2007, 2009; Petkova and Ehrsson, 2008). It is also known that there are varying degrees to which participants perceive this type of illusion and a certain percentage of people from the general population (also called "non-perceivers" in contrast to "perceivers") appear to be somewhat immune to the illusion. Research into individual differences in susceptibility to this and other somatosensory illusions is only starting to emerge, but it is this work which may be particularly interesting with regard to the laterality aspect of the illusion.

One of the first studies to examine individual differences in the RHI is that by Niebauer et al. (2002). The authors compared the susceptibility of strong right-handers with that of less strongly right-handed participants. Remarkably, it was found that the latter group reported a stronger experience and a tendency to a faster onset of the illusionary experience of incorporating a prosthetic hand into their body schema. The authors proposed that due to the assumed greater right hemisphere access, the less strongly handed were more "efficiently" able to update their body representation and thus experience the illusion to a greater extent.

Another recent exception to the lack of studies examining individual differences contributing to the extent to which sensory illusions are experienced is that by Tsakiris et al. (2011). The objective of this study was to determine the extent to which interoceptive abilities affect the integration of multiple sources of sensory information about the body. Similar to the studies examining participants with eating disorders cited above, Tsakiris et al. (2011) found that low interoceptive ability was associated with a stronger illusion generally and, more specifically, with greater proprioceptive drift, greater reduction in skin temperature of participant's own hand and greater feelings of ownership over the rubber hand. The authors conclude that the differential weighting of internal and external sources of information about the state of the body underlies the difference in susceptibility to the RHI. Greater weighting of right-hemispheric internal signals (Craig, 2002) may lead to a decrease in the extent to which the illusion is perceived. Unfortunately, no information about the laterality of the participants included in this study was given, and, at present, there are no investigations of the relationship between the degree of lateralization and interoceptive ability.

Finally, a study by Ocklenburg et al. (2010, p. 180) showed greater skin conductance response to a threat to the left hand as well as "a stronger subjective identification with the rubber hand on the left side" following the induction of the RHI compared to the response of the right hand. Interestingly, more recent work by the same group has shown that individuals affected by chronic regional pain syndrome, a condition characterized by unilateral deficient perception of static tactile stimuli, show a similar laterality effect (Reinersmann et al., 2013). Left-affected individuals reported a stronger RHI on their left hand compared to right-affected individuals. Furthermore, a significant negative correlation between the time passed since the onset of the disease and the strength of the illusion was only found for left-affected individuals. However, there is substantial clinical heterogeneity in chronic regional pain syndrome and bilateral cortical reorganization has also been reported (Marinus et al., 2011). Therefore, these latter findings will need to be interpreted cautiously.

Consistent with Ocklenburg et al.'s (2011) finding of an enhanced RHI for the left hand, it has also been found that neurologically healthy right-handers are particularly receptive to spontaneous sensations for their left hand compared to their right hand (Michael et al., 2012). In this last study, there was a significant difference between the left and right hand in the number of different spontaneous sensations (e.g., beat/pulse, tickle) reported after a ten second block as well as their intensity and spatial extent. Furthermore, visual attention modulated the effect spatially, by shifting the spontaneous sensations more distally (i.e., from the palm to the fingertips). Together the RHI and the spontaneous sensation finding suggest that the right hemisphere gives rise to a representation of the sensations arising from the left body half that is updated at a higher rate compared to tactile and visual signals from the right body half arriving at the left hemisphere. Both the weighting of internal to external signals within these representations of the right and left body half, and the weighting of right and left hemispheric contributions to the moment-to-moment representation of the body on the whole may contribute to individual differences in susceptibility to illusory percepts such as the RHI.

In summary, perceptual illusions pertaining to representations of the body are important in supplementing findings from the clinical literature because they enable the examination of intact systems in the healthy brain and body. They further illustrate the flexible boundary between what is perceived as part of our own body and that which is perceived as outside of our own body by inducing illusory shifts causing incorporation of space outside of the body and excorporation of body space. The RHI is

thus inherently spatial, acting on body location. A growing body of research shows that right hemispheric networks support the induction of the RHI and that individuals with a lower degree of lateralization are more susceptible to the illusion. Further, there is some evidence that individuals with low interoceptive abilities may experience the RHI more easily and vividly.

CONCLUSION

An ever-increasing amount of literature documents laterality effects with regard to space in vision (e.g., Brodie and Dunn, 2005; Cocchini et al., 2007), audition (e.g., Ocklenburg et al., 2010), the mental representation of numbers and the alphabet (e.g., Oliveri et al., 2004; Nicholls et al., 2008a) and even seemingly mundane tasks including Likert scale responses (Nicholls et al., 2006). Even though the hemispatial bias resulting from lateralization is small in magnitude in any one of these instances, its omnipresence means that the consequences are far-reaching. While external spatial representation has long been recognized as a lateralized system and many theories have been proposed as to the mechanism by which this division of function occurred (for some examples, see Davidson and Hugdahl, 2002), the spatial representation of abstract concepts and spatial representations created by modalities other than vision have only recently warranted attention.

Here, we summarized evidence from three different areas of body space literature which shows that laterality is a principle that governs the multimodal processing of this region of space also. Specifically, first evidence of right-hemispheric dominance for spatial body representations was shown to exist for simple, primary sensory representations of body space such as those utilized during pointing movements to one's own body and those at play in body illusions like the RHI, as well as more complex spatial representations of one's own body such as the distorted body space in individuals with eating disorders. It appears, therefore, that despite constituting a richer and more immediate spatial representation through the additional interoceptive component and the inescapable first-person perspective, body space is equivalent to external space in the sense of being supported by right-lateralized networks.

From the above observations we conclude the present review by proposing a working hypothesis stating that rather than many different spatial systems for different purposes, one main system may exist which allows for the action-oriented representation of one's own body and the parts of the external spatial world on which the action could potentially be applied. In other words, it may be most parsimonious and computationally efficient (see Gotts et al., 2013 for a summary of a similar argument regarding a computational benefit of lateralization) to possess one system for the processing of spatial information as a whole, be it for navigating from one side of the room to the other and avoiding collisions between one's own body and objects in the path, estimating the dimensions of a cup in relation to the size of one's own hand in order to grasp it or reaching for an itch on the back of the neck. Furthermore, it could be argued that due to the immediacy of spatial representations of one's own body, it is this representation that forms the vantage point for the perception of the world. In other words, not only might the size of one's neck determine what is perceived as in or outside of the wood, but the spatial representation of our own body may serve as the template for representing external (peri- and extrapersonal) space (see **Figure 1A**).

A related hypothesis commonly summarized under the heading of "embodied perception" similarly emphasizes the interdependency between the perception of the external world and the state of the perceiver's body (for a summary of prominent accounts, see, for example, Sebanz and Knoblich, 2010). For example, a widely cited piece of empirical evidence for this hypothesis is that the slope of a hill is apparently estimated as steeper by a metabolically challenged perceiver (who may be tired or may carry a heavy weight on their back) compared to a perceiver in a metabolically "neutral" state (Bhalla and Proffitt, 1999). While this account is complementary to the hypothesis forwarded as part of the present review, specifically with regard to metric representations of the body and their influence on the representation of the size of the environment (e.g., Linkenauger et al., 2011), two main differences exist. First, most theorizing that may be subsumed under the heading of embodied perception does not include a discussion of what the body itself constitutes (Proffitt and Linkenauger, 2013). Here, we conceptualize the body as a region of space and propose that the processing of this space may underlie similar principles as the processing of external space. Second, as evident from the example given above, the majority of the embodied perception literature is concerned with the influence of (the state of) the body on the visual perception of the world (e.g., Proffitt, 2013). We, in contrast, emphasize the importance of multisensory cues in the perception of body space and external space.

Support for the hypothesis of body space acting as a template for the action-oriented perception of external space can be found in the developmental trajectory of body and external spatial awareness, or the order in which these functions are acquired. For example, while children as young as 5 months can differentiate between the spatial pattern of self-produced movement and movement produced by another child (Schmuckler and Fairhall, 2001), depth perception and allocentric spatial encoding do not develop until children reach the toddling stage (e.g., Kermoian and Campos, 1988). Children who experience a developmental delay also often display deficits in spatial orientation, but no such deficits are present for the spatial representation of their own body (Herman and Siegel, 1978). Finally, (developmental) Gerstmann's syndrome is characterized not only by finger agnosia, but also by left–right disorientation and acalculia (Vallar, 2007; Rusconi et al., 2010) and may represent an instance where a deficit in the egocentric spatial representation (i.e., one's own hands) leads to difficulties in higher-order spatial representations (i.e., numbers) through the process of counting by using one's own hands, for example.

Returning to the examples of body space lateralization given in the preceding review, findings from the literature on hemispatial neglect are also congruent with the conjecture advanced here. As outlined above, hemispatial deficits of personal and extrapersonal space often occur together (e.g., Rorden et al., 2012). Importantly, isolated personal space deficits are rare, while instances of isolated deficits in extrapersonal space have been reported more often. The example of distorted space in individuals with eating disorders may similarly be interpreted as evidence of the inter-relatedness of

personal and external spatial representations, where distortions in the egocentric representation of body space may result in external spatial deficits downstream (see **Figure 1D**). Finally, body space illusions, such as the RHI and related phenomena, most strikingly the embodiment of a whole body of the other gender (Petkova et al., 2011) and of a child's body (Banakou et al., 2013), nicely illustrate the automaticity and impenetrability with which self-attribution takes place (Jeannerod, 2003). In the case of visual, tactile, and proprioceptive information arriving from roughly the same location in space, it appears that the representation of one's own body is adjusted to that location, and importantly, representations of external space are calibrated to it. For example, external objects appear to shrink in the face of an embodied large hand (Haggard and Jundi, 2009) or to grow in the face of illusory ownership over a small body (van der Hoort et al., 2011; Banakou et al., 2013; see **Figure 1E** for a schematic illustration of the scaling of peri- and extrapersonal space following the illusory embodiment of a small body).

In sum, we show hemispheric asymmetries to be evident in body representations at increasing levels of complexity from simple somatosensory and proprioceptive representations to higher-order representations. It should be noted that the examples of anorexia nervosa and the RHI reviewed here were selected due to the relatively high number of empirical studies examining these with regard to laterality. Many other conditions which may serve as examples of changes in body spatial representations (e.g., body dysmorphic disorder) could be equally informative here but were outside of the scope of this review. Based on findings from developmental, clinical, and experimental neuroscience, we propose the working hypothesis that spatial representations of one's own body may not only determine what is within one's reach or within one's neck of the woods, but serve as a basis for the action-oriented spatial perception of peri- and extrapersonal space. Related to higher cognitive functions, this may be interpreted more broadly as representations of the bodily self-constituting a template for representations of the external world.

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Lateralization of spatial information processing in response monitoring

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The current study aims at identifying how lateralized multisensory spatial information processing affects response monitoring and action control. In a previous study, we investigated multimodal sensory integration in response monitoring processes using a Simon task. Behavioral and neurophysiologic results suggested that different aspects of response monitoring are asymmetrically and independently allocated to the hemispheres: while efference-copy-based information on the motor execution of the task is further processed in the hemisphere that originally generated the motor command, proprioception-based spatial information is processed in the hemisphere contralateral to the effector. Hence, crossing hands (entering a "foreign" spatial hemifield) yielded an augmented bilateral activation during response monitoring since these two kinds of information were processed in opposing hemispheres. Because the traditional Simon task does not provide the possibility to investigate which aspect of the spatial configuration leads to the observed hemispheric allocation, we introduced a new "double crossed" condition that allows for the dissociation of internal/physiological and external/physical influences on response monitoring processes. Comparing behavioral and neurophysiologic measures of this new condition to those of the traditional Simon task setup, we could demonstrate that the egocentric representation of the physiological effector's spatial location accounts for the observed lateralization of spatial information in action control. The finding that the location of the physical effector had a very small influence on response monitoring measures suggests that this aspect is either less important and/or processed in different brain areas than egocentric physiological information.

Keywords: Simon task, response monitoring, spatial congruency, response evaluation, EEG, multisensory integration, proprioception

INTRODUCTION

In order to adequately interact with our environment, we constantly monitor our actions so that we can adjust them in case of undesired consequences (Logan, 1985; Stuss and Alexander, 2007; Fukui and Gomi, 2012). Properly doing so is a fairly complex endeavor because for a proper adjustment of the outcome, parameters of movements also need to be integrated in the process of response evaluation.

Given that different features (like speed, spatial position, applied force of the response, etc.) influence our movements, these parameters have to be integrated in the evaluation process (Praamstra et al., 2009; Fukui and Gomi, 2012; Gonzalez and Burke, 2013; Stock et al., 2013). We recently investigated the effects of multimodal sensory integration in response monitoring processes by recording an EEG during a Simon task (see Stock et al., 2013 for details) and demonstrated that both proprioception-based spatial information and efference-copy-based information on the motor execution are integrated in the supplementary motor area (SMA) during response monitoring and evaluation. Among other things, this brain region has been associated with the processing efference copies of motor commands (Neshige et al., 1988; Ikeda et al., 1995; Babiloni et al., 2001; Haggard and Whitford, 2004; Beaulé et al., 2012), egocentric proprioceptive information (Tarkka and Hallett, 1991; Hallett, 1994; Loayza et al., 2011), motor control (Angel, 1976; Wolpert and Flanagan, 2001; Allain et al., 2004; Yordanova et al., 2004; Feldman, 2009; Hoffmann and Falkenstein, 2010; Roger et al., 2010), and error monitoring (Peterburs et al., 2011). However, we obtained an unexpected pattern of hemispheric activation by asking the subjects to either cross their hands or keep them parallel while responding: in parallel hands, only the SMA contralateral to the responding hand showed a negative deflection of event-related potentials (ERPs) around the time of the response while the SMA ipsilateral to the responding hand showed a positivation. By contrast, the simple act of crossing one hand one over another reduced most of the differences in hemispheric activation/ERPs as the activity pattern of the hemisphere ipsilateral to the responding hand approximated that of the contralateral hemisphere. This suggests that in case of an unnatural posture (crossed hands) motor efference copies and motor proprioceptive information were allocated to the hemispheres according to different rules: efference-copy-based motor information seemed to be rather immutably locked to the hemisphere in which the motor command was initially processed. In contrast, the hemispheric allocation of proprioception-based spatial information was based on an external representation of space. As a result of these different lateralization mechanisms, crossing hands

(manually entering a "foreign" spatial hemifield) most probably resulted in a conflict, yielding an augmented bilateral activation and higher error rates.

Even though these findings seem to answer the question in which hemisphere the monitoring of motor and spatial information is allocated, the paradigm provided no possibility to determine whether the laterlized allocation of spatial information during response monitoring was influenced by internal (proprioceptive) information about the position of the physiologic effector (hand) or by external (egocentric) information about the position of the physical effector (button).

In the current study, we aimed at answering this question. For this purpose, we modified the Simon task by introducing a "double crossed" condition. While the regular Simon task only encompasses a parallel-hands and a crossed-hands condition, our new double crossed condition required the subjects to also operate crossed levers in half of the trials. As a consequence, the effect site (button) which was pressed when crossing hands in lever responses was in a different hemifield than the responding hand so that the button was the same as during a regular parallel hands button response (see **Figure 1** for further elucidation). Based on this dissociation of physiological effector (hand) and physical effect site (button), our question could be tackled: in case the spatial allocation of the hand is the relevant factor to the lateralization of response monitoring processes, parallel and crossed hands should yield comparable ERPs, irrespective of whether buttons or levers are used to respond. If however, the external effect site of the button was the critical feature, parallel-hands button responses should yield results similar to those of crossed-hands lever responses.

MATERIALS AND METHODS

SAMPLE

Right-handed participants ($N = 21$; ♀ = 11, ♂ = 10) were included in the study. The mean age was 23.2 years (min 19, max 32, SEM = 0.73) and none of the participants presented with a history of psychiatric or neurological disease. Handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971), yielding an average score of 0.81 (min 0.25, max 1.0, SEM = 0.05). All subjects gave written informed consent and were treated in accordance with the declaration of Helsinki. Each participant was reimbursed with 15€. The study was approved by the ethics committee of the medical faculty of the University of Bochum.

SETTINGS AND TASK

Because this study aims to extend previous findings reported by Stock et al. (2013), the settings and task were very similar to that study (see Stock et al., 2013 for details): participants were seated in front of a 17 in CRT computer monitor (at a distance of 57 cm) in a dimly lit and sound-attenuated room. Responses were made with four custom-made buttons mounted on a regular keyboard (see **Figure 1** for illustration).

The Simon task originally references the task used by Wascher et al. (2001). Throughout the whole task, a white fixation cross and two horizontally aligned white frame boxes were continuously displayed in the center of a dark blue screen. The two boxes were at the same vertical level as the fixation cross (1.1° distance between fixation cross and the inner border of the frames). Each trial began with the simultaneous presentation of a target stimulus (a yellow capital letter "A" or "B") and a noise stimulus (three white horizontal bars). Both target and noise stimuli were approximately

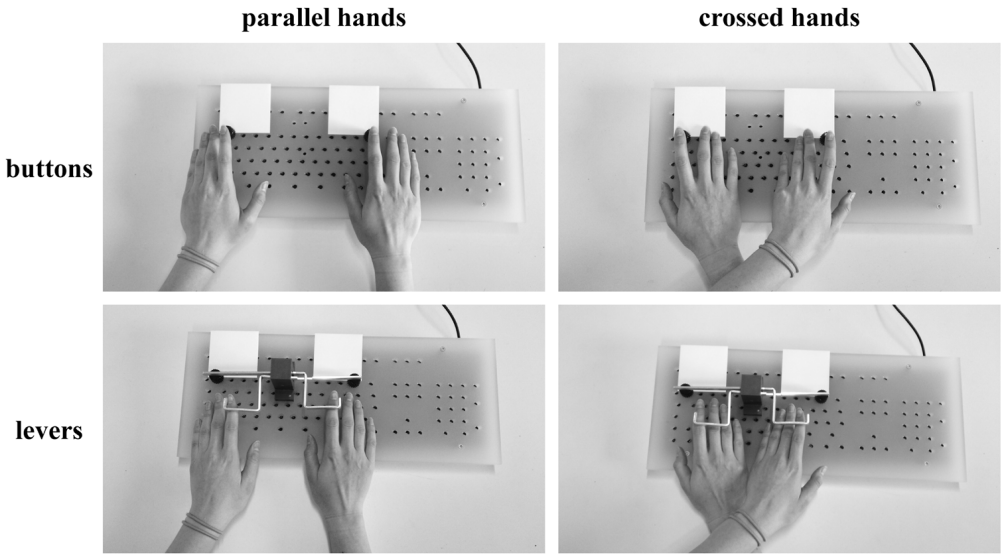


FIGURE 1 | The four different response conditions resulting from hand position (parallel vs. crossed) and button type (buttons vs. levers). When crossing hands, the participants were instructed to place the left arm ("marked" with two wristbands in the picture) on top of the right arm. In button responses, the physiological effector (hand) is in the same hemifield as the physical effector (button) so that their relevance for the hemispheric allocation of response monitoring processes cannot be determined. In contrast, the levers provide the necessary dissociation because the physical effector (button) is now located in a different hemifield than the physiological effector (hand). For mechanical reasons, buttons had to be pressed while levers had to be lifted.

0.5° wide and 0.6° high and presented within the two opposing white boxes. After 200 ms, the stimuli disappeared and the trial was ended by the first (button press) response. If the participants did not respond within the first 500 ms after the onset of the trial, a speed-up sign (containing the German word "Schneller!" which translates to "Faster!") was presented above the stimuli until the end of the trial. In case no response was given, the trial automatically ended 1700 ms after its onset and was coded as a "miss." The response–stimulus intervals (RSIs) varied randomly and ranged between 2000 and 2500 ms.

The experiment consisted of eight blocks, each comprising 160 trials. The four stimuli ("A" on the left side/"A" on the right side/"B" on the left side/"B" on the right side) were randomized and occurred equally often, resulting in 40 trials per condition and block. For all blocks, participants were instructed to respond using the left index finger whenever the target stimulus was an "A" and to respond using the right index finger whenever the target stimulus was a "B" (in both cases irrespective of the target's location on the screen). In blocks 1, 3, 5, and 7 they were asked to respond with parallel hands while they were asked to cross their hands (placing the left arm above the right arm) in blocks 2, 4, 6, and 8. In addition to the setup of our previous study (Stock et al., 2013), participants were requested to respond by pressing the buttons in blocks 1, 2, 5, and 6 while levers had to be used in blocks 3, 4, 7, and 8 (see **Figure 1**). Hence, there were two blocks for each combination of hand position (parallel/crossed) and button type (buttons/levers). Following from this, there were equal numbers of congruent and incongruent trials (classified depending on whether the responding hand was placed in the same hemifield as the target stimulus).

EEG RECORDING DATA PROCESSING

As for the settings and task, EEG data recording and data processing are very similar to techniques used for our previous publication (see Stock et al., 2013 for details): an EEG was recorded from 65 Ag–AgCl electrodes at standard positions (international 10–20 system) while the participants were performing the task. Electrode impedances were kept below 5 kΩ. During recording, a filter bandwidth of 0–80 Hz was applied and EEG data was recorded with a sampling rate of 1000 samples per second against a reference at electrode FCz. After recording, the data was downsampled to 256 Hz and an IIR filter (notch at 50 Hz; high-pass at 0.5 Hz and low-pass at 18 Hz, using a slope of 48 dB/oct each) was applied. Subsequently, technical artifacts and irregular muscular artifacts (e.g., jaw clenching) were removed during a visual raw data inspection. Uniform artifacts (primarily blinks, eye movements and pulse artifacts) were removed by means of an independent component analysis (ICA) applying the infomax algorithm.

For stimulus-locked event-related lateralizations (ERLs), segments were formed for the different conditions. Epochs started 200 ms before the stimulus presentation (which was set to time point zero) and ended 1200 ms after the response, resulting in a total epoch length of 1400 ms. For the analysis of response-locked event-related potentials (ERPs), segments were formed for the different conditions. Epochs started 1200 ms before the response (which was set to time point zero) and ended 1200 ms after the response, resulting in a total epoch length of 2400 ms.

Independent of the locking point (stimulus or response), only trials that had been correctly answered within the first 1500 ms after the onset of the stimulus presentation were included. Furthermore, an automated artifact rejection removed amplitudes above 100 μV and below −100 μV as well as activity of less than 0.5 μV over a time span of 100 ms or more. Subsequently, a current source density (CSD) transformation was applied to eliminate the reference potential (Perrin et al., 1989; Nunez and Pilgreen, 1991; Nunez et al., 1997).

For the analysis of stimulus-locked ERLs/N2pc, a baseline correction from −200 to 0 ms was run before the segments of the different conditions were averaged. Based on the topographic distribution of the activity and the literature relevant to this task, ERLs were formed for electrodes PO7 and PO8 (Praamstra and Oostenveld, 2003; Wiegand and Wascher, 2005; Verleger et al., 2012; Cespón et al., 2013; Stock et al., 2013). For this purpose, the values of the hemisphere ipsilateral to the target stimulus site were subtracted from the values of the hemisphere contralateral to the target stimulus site (PO7–PO8 for stimuli presented on the right side and PO8–PO7 for stimuli presented on the left side) and averaged for both hands. For statistical analyses, we extracted the mean electrode activity between 180 and 270 ms (the time frame was based on the negative peak and differences between the conditions; see **Figure 2**).

For the analysis of response-locked ERPs, a baseline correction from −1200 to −800 ms was run before the segments of the different conditions were averaged. Based on our previous study, we decided to quantify the response-locked ERPs at electrodes FC1 and FC2 because these electrodes have been shown to optimally depict response evaluation differences/changes in SMA activity between the different conditions of this task (see Coles, 1989; Leuthold, 2011; Stock et al., 2013 for details). For statistical analyses, we extracted the mean electrode activity between −60 and 60 ms (the time frame was based on the differences between the conditions; see **Figure 3**).

STATISTICAL ANALYSIS

Behavioral data (RTs and the number of hits/correct responses) were analyzed using repeated-measures analyses of variance (ANOVA). "Button type" (button responses vs. lever responses), "hand position" (parallel hands vs. crossed hands), and "congruency" (congruent vs. incongruent; codes whether the target stimulus was presented on the side where the responding hand was placed) were used as within-subjects factors. The electrophysiological stimulus-locked data was analyzed using repeated-measures ANOVA with the within-subjects factors "button type," "hand position," and "congruency." Because ERLs are based on the difference between the hemisphere contralateral and ipsilateral to the stimulus presentation site, there was no factor for side/hemisphere. The electrophysiological response-locked data was analyzed in similar fashion using a repeated-measures ANOVA with the within-subjects factors "button type," "hand position," "congruency," and "executive hemisphere" (electrode above the hemisphere responsible for the motor execution of the response vs. electrode above the hemisphere irresponsible for the motor execution of

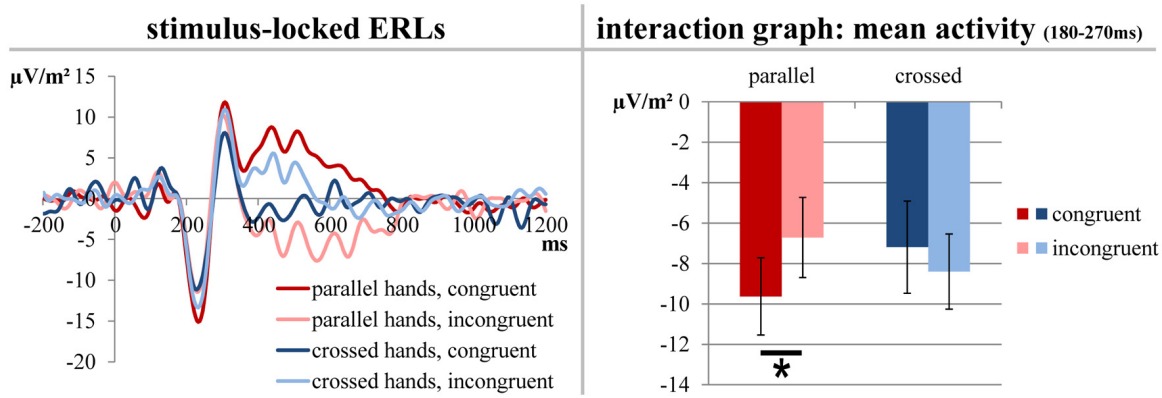


FIGURE 2 | The stimulus-locked ERLs for electrodes PO7/PO8 obtained by subtracting the ERP curve of the hemisphere ipsilateral to the stimulus presentation site from the ERP curve contralateral to the stimulus presentation site. Only factors yielding significant results are depicted. The left side of the figure shows the course of the curves; time point zero denotes the onset of stimulus presentation. The right part of the figure elucidates the significant differences found between the mean activity values which average the time span from 180 to 270 ms. The error bars indicate the respective SEMs; significant differences are marked with an asterisk.

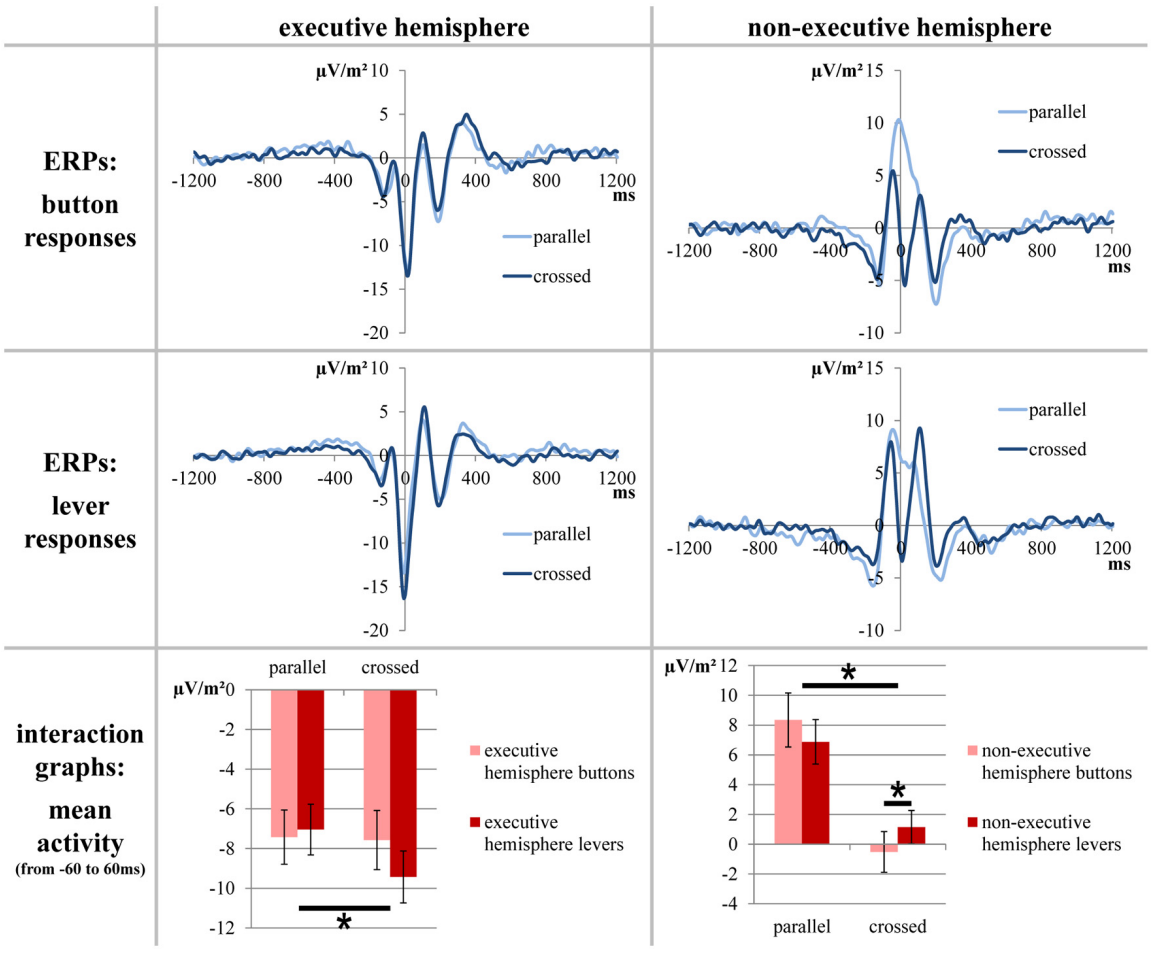


FIGURE 3 | The stimulus-locked ERPs for electrodes FC1/FC2. Only factors yielding significant results are depicted. The upper parts of the figure show the course of the curves; time point zero denotes the response. The lower part of the figure elucidates the significant differences found between the mean activity values which average the time span from −60 to 60 ms. The error bars indicate the respective SEMs; significant differences are marked with an asterisk.

the response). Greenhouse–Geisser-correction was used whenever necessary. All *p*-levels for *post hoc t*-tests were adjusted using Bonferroni correction. Effect sizes were given as the proportion of variance accounted for (η^2). As a measure of variability, the standard error of the mean (SEM) together with the mean values was given.

RESULTS

BEHAVIORAL DATA

Accuracy

A repeated-measures ANOVA of the percentage of hits (within-subjects factors "button type," "hand position," and "congruency") revealed a significant main effect for "hand position" [$F(1,20) = 4.571$; $p = 0.045$; $\eta^2 = 0.186$] with more correct answers in parallel-hands trials (89.0% ± 1.653) than in crossed-hands trials (86.6% ± 1.506). There was also a significant main effect for "congruency" [$F(1,20) = 1.197$; $p < 0.001$; $\eta^2 = 0.792$] with more correct answers in congruent trials (91.8% ± 1.336) than in incongruent trials (83.7% ± 1.735). There was also a significant interaction of "button type" × "congruency" [$F(1,20) = 19.845$; $p < 0.001$; $\eta^2 = 0.498$]. *Post hoc t*-tests revealed that buttons yielded more correct responses than levers in congruent trials [$t(20) = 2.255$; $p = 0.036$; buttons: 94.5% ± 0.695 and levers: 89.2% ± 2.434] but not in incongruent trials [$t(20) = -0.217$; $p = 0.831$]. Furthermore, there was a significant interaction of "hand position" × "congruency" [$F(1,20) = 9.691$; $p = 0.005$; $\eta^2 = 0.326$]. *Post hoc t*-tests revealed that there were more correct answers in parallel-hands trials than in crossed-hands trials only in incongruent trials [$t(20) = 3.163$; $p = 0.005$; parallel: 86.0% ± 1.904 and crossed: 81.5% ± 1.848] but not in congruent trials [$t(20) = 0.262$; $p = 0.796$].

Response times

A repeated-measures ANOVA of the RTs of correct responses (within-subjects factors "button type," "hand position," and "congruency") revealed significant main effects for all three factors: "hand position" significantly differed [$F(1,20) = 7.365$; $p = 0.013$; $\eta^2 = 0.269$] with correct parallel-hands response being faster (442.4 ms ± 9.579) than correct crossed-hand responses (452.1 ms ± 10.247). There was also a significant main effect for "button type" [$F(1,20) = 27.783$; $p < 0.001$; $\eta^2 = 0.581$] with correct button responses being faster (436.1 ms ± 8.958) than correct lever responses (458.4 ms ± 10.914). The significant main effect for "congruency" [$F(1,20) = 73.787$; $p < 0.001$; $\eta^2 = 0.787$] was based on faster responses in congruent trials (435.8 ms ± 10.048) than in incongruent trials (458.7 ms ± 9.643). There were also a significant interaction of "button type" × "congruency" [$F(1,20) = 29.994$; $p < 0.001$; $\eta^2 = 0.600$] and a significant threefold interaction of "hand position" × "button type" × "congruency" [$F(1,20) = 7.547$; $p = 0.012$; $\eta^2 = 0.274$]. A *post hoc* repeated-measures ANOVA confined to lever responses only showed a significant main effect for "congruency" [$F(1,20) = 21.492$; $p < 0.000$; $\eta^2 = 0.518$] with RTs in congruent trials being faster (450.9 ms ± 11.724) than RTs in incongruent trials (465.8 ms ± 10.294). In contrast, the *post hoc* repeated measures ANOVA confined to the button responses found a significant main effect for "congruency" [$F(1,20) = 117.445$; $p < 0.001$; $\eta^2 = 0.854$; congruent: 420.6 ms ± 8.632 and incongruent: 451.5 ± 9.490] as well as for "hand position" [$F(1,20) = 9.285$ $p = 0.006$; $\eta^2 = 0.316$; parallel: 428.7 ms ± 8.614 and crossed: 443.4 ± 9.902]. However, none of the ANOVAs showed a significant interaction ($p \geq 0.129$).

Summary of behavioral results

Briefly summing up the behavioral results, significant interactions show that the subjects hit rate was differently modulated across congruency: in congruent trials only, button responses had higher hit rates than lever responses while in incongruent trials only, parallel-hand responses had higher hit rates than crossed-hand responses.

Furthermore, a threefold interaction indicated that hit RTs were modulated by button type, congruency, and hand position: while congruency modulated the RT in both button and lever responses (congruent faster than incongruent), only button response RTs were additionally modulated by hand position (parallel faster than crossed).

NEUROPHYSIOLOGICAL DATA

Stimulus-locked data

Stimulus-locked data at electrodes PO7 and PO8 are depicted in **Figure 2**.

A repeated measures ANOVA (within-subjects factors "button type," "hand position," and "congruency") of the mean ERL activity at electrodes PO7 and PO8 (stimulus-locked data; averaged from 180 to 270 ms) was run. It yielded a significant interaction of "hand position" × "congruency" [$F(1,20) = 7.968$, $p = 0.011$, $\eta^2 = 0.285$]. *Post hoc t*-tests showed that congruent trials produced a bigger/more negative ERL (−9.629 $\mu V/m^2$ ± 1.913) than incongruent trials (−6.712 $\mu V/m^2$ ± 1.980) in parallel-hand trials [$t(20) = -3.669$, $p = 0.002$] but not in crossed-hand trials [$t(20) = 1.301$, $p = 0.208$; see **Figure 2** for visualization].

Response-locked data

Response-locked ERPs at electrodes FC1 and FC2 are depicted in **Figure 3**.

A repeated measures ANOVA (within-subjects factors "button type," "hand position" "executive hemisphere," and "congruency") of the mean activity at electrodes FC1 and FC2 (response-locked data; averaged from −60 to 60 ms) was run. It yielded a significant main effect for "hand position" [$F(1,20) = 43.474$; $p < 0.001$; $\eta^2 = 0.685$] with a positive mean activity for correct parallel-hands responses (0.189 $\mu V/m^2$ ± 1.296) and a negative mean activity for correct crossed-hands responses (−4.094 $\mu V/m^2$ ± 1.197). The main effect for "executive hemisphere" was also significant [$F(1,20) = 189.227$; $p < 0.001$; $\eta^2 = 0.904$] with a negative mean activity over the executive hemisphere (−7.867 $\mu V/m^2$ ± 1.236) and a positive mean activity over the non-executive hemisphere (3.962 $\mu V/m^2$ ± 1.321) during correct responses. There was a significant interaction for "hand position" × "congruency" [$F(1,20) = 5.220$; $p = 0.033$; $\eta^2 = 0.207$]. However, this interaction did not survive *post hoc* testing. *Post hoc t*-tests revealed that congruent and incongruent trials neither differed in the parallel-hands condition [$t(20) = -1.869$; $p = .076$] nor in

the crossed-hands condition [$t(20) = 1.523$; $p = 0.143$]. Likewise, there were significant differences between hand positions in both congruent [$t(20) = 4.775$; $p < 0.001$] and incongruent trials [$t(20) = 5.957$; $p < 0.001$]. Furthermore, there was a significant interaction for "hand position"×"executive hemisphere" [$F(1,20) = 61.960$; $p < 0.001$; $\eta^2 = 0.756$]. Finally, there was a significant threefold interaction for "hand position" × "executive hemisphere" × "button type" [$F(1,20) = 35.912$; $p < 0.001$; $\eta^2 = 0.642$]. A *post hoc* repeated-measures ANOVA confined to the executive hemisphere only showed significant main effect for hand position [$F(1,20) = 5.760$; $p = 0.026$; $\eta^2 = 0.224$] with parallel hands evoking a smaller mean amplitude ($-7.233\,\mu V/m^2 \pm 1.217$) than crossed hands ($-8.500\,\mu V/m^2 \pm 1.308$) in correct responses. The *post hoc* repeated measures ANOVA confined to the non-executive hemisphere found a significant main effect for "button type" [$F(1,20) = 62.058$; $p < 0.001$; $\eta^2 = 0.756$; buttons: $3.912\,\mu V/m^2 \pm 1.504$ and levers $4.012\,\mu V/m^2 \pm 1.232$] and significant interaction of "button type" × "hand position" [$F(1,20) = 10.191$ $p = 0.005$; $\eta^2 = 0.338$]. *t*-Tests revealed that in the non-executive hemisphere, there was a difference between button types for correct crossed-hand responses [$t(20) = -2.331$; $p = 0.030$ with buttons $-0.522\,\mu V/m^2 \pm 1.368$ and levers $1.149\,\mu V/m^2 \pm 1.119$] but not for parallel-hand responses [$t(20) = 1.384$; $p = 0.182$; see **Figure 3** for visualization].

Summary of neurophysiological results

Briefly summing up the electrophysiological results, the stimulus-locked ERLs of correct responses were modulated by an interaction of congruency and hand position: only in parallel-hand responses, congruent trials evoked significantly more negative ERLs than incongruent trials. Furthermore, the response-locked ERPs of correct responses were modulated by an interaction of button type, hand position, and hemisphere (but not by congruency): in the non-executive hemisphere, button and lever responses differed from each other when hands were crossed (but not when they were parallel). By comparison, the mean amplitudes of the executive hemisphere only differed between parallel and crossed-hand responses.

DISCUSSION

The current study aimed at determining whether the location of an internal/physiologic effector (hand) or the location of an external, physical effector (response button) accounts for the previously observed asymmetric lateralization of spatial aspects of response monitoring processes (Stock et al., 2013).

The results (especially the interaction pattern observed in the response-locked ERP data) suggest that the spatial location of the physiologic effectors accounts for the largest part of the observed changes in the hemispheric allocation of spatial information during response monitoring. In order to elucidate the rationale behind this interpretation, we would like to explain the theoretical background of our experimental manipulation: the basic assumption behind the additional factor "button type" is that "each hemisphere preferentially processes and integrates the contralateral egocentric and allocentric spatial information" (Zhou et al., 2012). Following from this, trials with button responses provide a "baseline" measurement because the hand and button involved in a response are always located in the same spatial hemifield. Differences between the two hand positions (parallel vs. crossed) can be attributed to spatial properties of the effectors, but the effectors (hand vs. button) cannot be told apart. In contrast to this, trials with lever responses provide the measurement of our "experimental manipulation" because in this condition, the responding hand and the button pressed are always located in opposing spatial hemifields. Hence, the influence of the different effectors can be distinguished by comparing baseline and experimental manipulation/button and lever trials: influences exerted by the physiologic effector/the location of the hand should yield identical or at least similar result for both button types (i.e., parallel-hand button responses ≈ parallel-hand lever responses and crossed-hand button responses ≈ crossed-hand lever responses). In contrast to this, influences exerted by the physical effector/the location of the button should yield opposing or at least different results for the two button types (i.e., parallel-hand button responses ≈ crossed-hand lever responses and crossed-hand button responses ≈ parallel-hand lever responses).

The first option is basically what was observed in the response-locked ERPs. Such fronto-central ERPs are known to reflect response monitoring and evaluation processes and are most likely generated within the SMA, anterior cingulate cortex, and adjacent areas (Macar et al., 1999; Luu and Tucker, 2001; Beste et al., 2010a,b, 2012; Roger et al., 2010; Wascher and Beste, 2010). In our previous study, we could demonstrate the response-locked ERPs quantified in this study originate within the SMA and are sensitive to the spatial allocation of the effector (Stock et al., 2013). As described above, we aimed at identifying the effector (physical or physiological) by comparing button and lever response conditions. As can be seen in the top row ("button responses") of **Figure 3**, placing the effectors in their usual hemifield yields a positivation of the response-locked ERP over the non-executive hemisphere. By contrast, placing the effectors in the "foreign" hemifield yields a negativation of the response-locked ERP over the non-executive hemisphere so that it resembles the course of the ERP curve over the executive hemisphere. Furthermore, it can be noted that the ERP over the non-executive hemisphere is more negative when the effectors are placed in the contralateral hemifield. A repeated-measures ANOVA was run to compare lever responses to button responses. Due to the interactions of factors, the main effects of hand position and hemisphere cannot be subject to interpretation. We would however like to point out that there was no main effect of button type. Hence, there was no basic fundamental difference between buttons and levers which is in favor of assuming the hands to be the relevant effectors. Two interactions are important: first, there was an interaction of hand position and congruency. Because both *post hoc* tests yielded significant differences between the hand positions (each parallel > crossed), the finding only differed quantitatively between congruent and incongruent trials. Second, there was a threefold interaction of button type, hand position, and hemisphere. This interaction is crucial when trying to answer the question of which effector (hand or button) accounts for lateralization of spatial aspects of response monitoring processes. The button

type had no effect on the executive hemisphere that always processes efference-copy-based information of the motor aspects of the response and information on spatial properties of the response in half of the trials. In the non-executive hemisphere, the button type only had an effect in crossed hands (lever responses yielding more positive ERPs than button responses), but not in parallel hands.

Our interpretation is as follows: the fact that the activation of the non-executive hemisphere does not differ in parallel-hand responses suggests that this hemisphere does not contribute to response monitoring/process spatial information in neither button nor lever response trials. This suggests that the location of physiological effectors (the hands which stayed within their "natural" hemifield) accounts for the lateralization of response monitoring processes and that the physical effector (the location of the button) does not. The non-executive hemisphere difference between buttons and levers in crossed hands is not strictly in line with the assumption that only the hands are responsible for the hemispheric allocation of spatial information during response monitoring. Yet, it is unlikely that the physical effector (button) plays a major role in the allocation of response monitoring processes. The reason for this is that based on the explanations above, one would expect a "reversal" of parallel and crossed non-executive hemisphere ERPs across the button types. In case of an allocation based on the location of the physical effector, lever responses should produce a positive peak in crossed hands and a negative peak in parallel hands (crossed > parallel) over the non-executive hemisphere. This criterion is not fulfilled since both in button and in lever responses; parallel hands yield a more positive ERP than crossed hands (see **Figure 1**). Because of the different polarity of ERP peaks around the time of the response, we based the statistical analysis on mean activity measures. While these measures can depict differences between the epochs over which the ERP data was averaged, they unfortunately cannot account for the course of the curves within these epochs. Yet, we obtained no convincing statistical results in favor of a physical effector approach and the grand averages (**Figure 3**) further support the assumption that the physiologic effector (hand) determines the allocation of spatial response monitoring processes: despite the detected differences, the course of the ERP curves of crossed-hand lever responses is very similar to that of crossed-hand button responses while both crossed-hand conditions markedly differ from the course of parallel-hand responses.

Furthermore, the behavioral results of this study are line with previous findings on this paradigm (e.g., Wiegand and Wascher, 2005; Leuthold, 2011) suggesting that the task was correctly implemented/worked as intended. Both hit rates and RTs were modulated by the hand position as well as the spatial congruency of the stimulus presentation site and the location of the responding hand. In all significant main effects and interactions, parallel-hand responses yielded a better (more accurate/faster) performance than crossed-hand responses and congruent trials yielded better results than incongruent trials. Matching results were obtained for the stimulus-locked ERLs/N2pc. As expected, the ERLs showed an interaction of hand position and congruency (see Praamstra and Oostenveld, 2003; Wiegand and Wascher, 2005; Böckler et al., 2011; Leuthold, 2011; Verleger et al., 2012). For the ERLs, there was no effect of button type whatsoever. Since stimulus–response congruency had been defined with respect to the location of the hand (not the button), this finding clearly indicates that external/physical effectors do not seem to have an influence on congruency and on early attentional processing and/or filtering (Luck and Hillyard, 1994; Böckler et al., 2011; Leuthold, 2011; Verleger et al., 2012).

From this study, it can be concluded that the spatial location of physiologic effectors (in our case, this would be the hands) plays a major role in the asymmetrical allocation of response monitoring processes: whenever the physiologic effectors enter a "foreign" hemifield, the hemisphere contralateral to this hemifield seems to handle information on spatial aspects of the response. By comparison, the location of the physical effector (in our case, this would be the buttons) plays a minor role. Yet, the possibility that it still contributes to response monitoring processes cannot be ruled out completely. Furthermore, these findings allow for the conclusion that potentially different action goals of button and lever responses do not substantially influence the lateralized allocation of response monitoring processes (compare to Buhlmann et al., 2007). Our study extends the established fact that each hand operates "in its own egocentric space" (Haggard et al., 2000) by demonstrating that egocentric space continues to play a role in the subsequent processes of response monitoring and evaluation. Also, our results are in line with the findings that proprioceptive (Allain et al., 2004) and internal sensorimotor information is used for response evaluation (Fukui and Gomi, 2012) and that each hemisphere preferentially processes information from the contralateral hemifield (Zhou et al., 2012).

AUTHOR CONTRIBUTIONS

Both authors contributed to the design of the experiment, data collection, the interpretation of results, and to the written manuscript.

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Hemispheric specialization in selective attention and short-term memory: a fine-coarse model of left- and right-ear disadvantages

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Serial short-term memory is impaired by irrelevant sound, particularly when the sound changes acoustically. This acoustic effect is larger when the sound is presented to the left compared to the right ear (a left-ear disadvantage). Serial memory appears relatively insensitive to distraction from the semantic properties of a background sound. In contrast, short-term free recall of semantic-category exemplars is impaired by the semantic properties of background speech and is relatively insensitive to the sound's acoustic properties. This semantic effect is larger when the sound is presented to the right compared to the left ear (a right-ear disadvantage). In this paper, we outline a speculative neurocognitive fine-coarse model of these hemispheric differences in relation to short-term memory and selective attention, and explicate empirical directions in which this model can be critically evaluated.

Keywords: ear-advantage, hemispheric asymmetry, distraction, short-term memory, left-ear disadvantage, right-ear disadvantage

One way in which our understanding of hemispheric specialization has been advanced is through the study of auditory processing (Cherry, 1953; Broadbent, 1958; Hugdahl, 2003; Hugdahl et al., 2009). Specifically, the combination of weaker ipsilateral pathways and stronger contralateral pathways within the auditory system results in the contralateral processing of sound. Input to the left ear, for example, has privileged access to the right hemisphere (RH), whereas input to the right ear has privileged access to the left hemisphere (LH). Sound, such as speech, is therefore predominately processed by the opposite hemisphere to its presentation source. These hemispheric differences result in the *right-ear advantage* in identifying or shadowing linguistic target-stimuli that are presented to the right-ear/LH (Kimura, 1961, 1967; Broadbent and Gregory, 1964; Studdert-Kennedy and Shankweiler, 1970) and the *left-ear advantage* for the processing of non-linguistic sound presented to the left-ear/RH (Tervaniemi and Hugdahl, 2003; Poeppel et al., 2004), especially with binaural sound presentation, although ear-advantages with monaural presentation have also been shown (Bradshaw et al., 1981). In this article, we review existing work on how this hemispheric asymmetry influences selective attention and short-term memory in the context of cross-modal auditory distraction.

CROSS-MODAL DISTRACTION

THE IRRELEVANT SOUND EFFECT (AND RIGHT HEMISPHERE PROCESSING)

The irrelevant sound effect refers to the observation that short-term memory for the correct serial order of a set of sequentially presented visual items (visual-verbal serial recall) is disrupted by the mere presence of background sound. Despite explicit instruction to ignore the sound, error rates can increase by up to 50% (Ellermeier and Zimmer, 1997). Two pre-requisites for irrelevant sound to produce substantial disruption are, first, that the focal task involves serial rehearsal of the to-be-recalled (TBR) items (Beaman and Jones, 1997), and second, that the irrelevant sound demonstrates appreciable acoustic variation from one sound element to the next (Jones and Macken, 1993). For example, if participants are required to maintain the serial order of TBR items, auditory changing-state sequences (e.g., "a b a b a b a") are typically more disruptive than steady-state sound sequences (e.g., "a a a a a a a"), the *changing-state effect*. However, if participants are required to identify which member of a well-known set (e.g., Weekdays) that is not presented – the *missing-item task* – the changing-state effect does not emerge (Beaman and Jones, 1997). The theoretical reason for this is that the missing-item task does not require seriation of the TBR items, and so there is no conflict between the order information in the changing-state sequence and the processes that are required to fulfill the task. The combination of these two pre-requisites suggests that the changing-state effect is a function of the similarity between two sets of order processes: The deliberate processing of the order of the TBR items and the involuntary processing of the order between successive and perceptually discrete sound events (for a review, see Jones et al., 2010).

It does not matter whether the changing-state sequence consists of speech utterances or pure tones (e.g., Jones and Macken, 1993), the magnitude of disruption is rather a function of the sound's acoustic variation (Jones et al., 2000), which suggests that the sound's phonological and semantic content plays little if any role, although this is still the subject of debate (e.g., Bell et al.,

2011). Item identity typically plays a more subservient role than acoustic variation (Jones et al., 2010), but serial recall of visual digits is more greatly impaired by irrelevant digits than irrelevant consonants if the order of the irrelevant digits is different (i.e., incongruent) to the order of the TBR digits, but not when it is similar (congruent; Hughes and Jones, 2005; Bell et al., 2011).

The changing-state effect has been used as an analytic tool to study hemispheric biases for passive processing of irrelevant sound. For example, Hadlington et al. (2004) found that speech utterances (Experiments 1a and 2a) and sine wave tones (Experiments 1b and 2b) impair serial memory to a greater extent when presented to the left-ear-only, relative to right-ear-only presentation and presentation to both ears. This *left-ear disadvantage* was later replicated in the context of a mental arithmetic task (cf. Banbury and Berry, 1998), but was not found in the context of a missing-item task (Hadlington et al., 2006). Moreover, the left-ear disadvantage was greater in magnitude when the irrelevant sequence conveyed acoustic variation, such as pitch changes, and varied inter-stimulus intervals, but it was absent when the sound stream contained little acoustic variation (such as a repetition of a single utterance). Collectively, serial short-term memory is more impaired from sound with a left-ear source, and it does not matter if that sound has lexico-semantic content or not.

These findings cohere nicely with the notion that the RH plays a prominent role in the obligatory processing of the acoustic features rather than the item identity/content within the irrelevant sound streams (Zatorre et al., 1994; Grimshaw et al., 2003; Poeppel et al., 2004): The RH specialization for processing serial information turns into a *disadvantage* when sound is to-be-ignored and the focal task also requires seriation.

ITEM BASED DISTRACTION (AND LEFT HEMISPHERE PROCESSING)

As discussed above, acoustic variation appears to interfere selectively with serial memory in the RH, due to a conflict between deliberate order processes and an automatic analysis of acoustic change in the unattended sound. Both behavioral and neuroimaging studies propose that order and item information are supported by separate cognitive representations (for a review, see Marshuetz, 2005), which suggests that background sound could selectively impair item memory, just as it selectively impairs serial memory in the RH. This is the question we turn to next.

The LH appears to dominate language/semantic processing. For example, little lexical-semantic analysis of deliberately ignored speech is thought to take place in the RH (Beaman et al., 2007) and the LH responds to lexical-semantic information of auditory word stimuli (Zahn et al., 2000). Moreover, memory for verbal material is LH localized (e.g., Smith et al., 1996; Baddeley, 2003) and the right-ear advantage in dichotic listening (e.g., Hugdahl et al., 2009) supports privileged linguistic processing in the LH. Taken together, in the context of tasks that require semantic processing, which predominantly depend on the LH, background speech might actually be more disruptive when presented to the right ear. This hypothesis has recently received some support (Sörqvist et al., 2010).

Sörqvist et al. (2010) used a paradigm wherein TBR visual lists comprise exemplars that are members of the same semantic category (e.g., Fruit). To-be-ignored spoken words that are taken from the same semantic category as the TBR items (e.g., other Fruit) produce greater disruption to free recall than to-be-ignored words from a different semantic category (e.g., Tools): the *between-sequence semantic similarity effect* (Marsh et al., 2008). This effect is indexed as fewer correct recalls of visual-targets and greater false recall (e.g., of words that were spoken in the background). The between-sequence semantic similarity effect is found when speech is presented to the right-ear/LH but not when it is presented to the left-ear/RH (Sörqvist et al., 2010). Importantly, this *right-ear disadvantage* is only found when the task is to recall the items in *free* order (Experiments 1 and 3), not when they must be recalled in order of presentation (Experiment 2).

Thus, task requirement appears to determine when a left-ear or a right-ear disadvantage is found. Verbal item memory, localized to the LH, is more impaired when task-irrelevant linguistic information is presented to the right-ear/LH, whereas serial order memory, predominantly localized to the RH, is more impaired by acoustically varying sound presented to the left-ear/RH. Interestingly, the ear-*disadvantages* have been shown in the context of monaural sound presentation, whereas the ear-*advantages* are typically found with binaural presentation. A right-ear advantage is found with monaural presentation, however, when several sound streams are presented simultaneously to the same ear, and there is a need to resolve stimulus competition (Bradshaw et al., 1981). Taken together with the cross-modal effects, the ear asymmetries in monaural presentation may arise because of the competition between processing streams.

False recall

In the context of free recall, spoken words that are related (e.g., Tools) to the TBR items (e.g., Tools) typically produce more false recall (of items that belong to the target category, but were not part of the target list) than unrelated spoken words (e.g., Occupations; Marsh et al., 2008). This effect is greater for right-ear/LH presentation (Sörqvist et al., 2010). Initially, these results appear consistent with the model offered by Beaman et al. (2007) wherein it is assumed that right-ear input increases the capacity of speech to interfere with the semantic processes in the LH, whereas this capacity is attenuated for left-ear input. However, Sörqvist et al. (2010) found that *unrelated* speech presented to the left-ear/RH resulted in *more* false recall than unrelated speech presented to the right-ear/LH (i.e., a left-ear disadvantage for the effect of unrelated speech on false recall). Moreover, despite generation of fewer intrusions with unrelated speech presented to the right-ear/LH, those that emerged were generally greater in output-dominance (e.g., DOG is a more dominant member than LIZARD of the category "four-legged animal"). The finding that *unrelated* speech presented to the left-ear/RH has systematic effects on false recalls suggests some lexical-semantic processing of irrelevant speech within the RH.

UNDERSTANDING THE PATTERN OF INTRUSIONS ACROSS THE HEMISPHERES

Hemispheric asymmetries in (attended) semantic processing are well documented. For example, Beeman and colleagues (Beeman et al., 1994; Beeman and Chiarello, 1998; Bowden and Beeman, 1998; Beeman and Bowden, 2000; Bowden and Jung-Beeman,

2003) suggest that the LH is particularly attuned to fine processing, activating a restricted semantic network comprising of a small number of closely related concepts. In contrast, the RH specializes in coarse processing (Tervaniemi and Hugdahl, 2003) activating a widespread, diffuse array of associates.

This fine-coarse processing mechanism is supported by evidence from semantic priming. Greater summation priming from three weakly-related, centrally-presented, prime words (e.g., *foot-cry-glass*) is found when the target word (e.g., *cut*) is presented to the left visual-field/RH as opposed to the right visual-field/LH (Beeman et al., 1994). In contrast, directly related primes (e.g., *scissors*) show greater priming than summation primes when targets are presented in the right visual-field/LH. The idea is that the RH weakly activates large semantic fields, which overlap, and therefore, although each semantic field is only weakly activated, this overlap allows the weakly related concepts to activate more strongly, reaching threshold. In contrast, the LH strongly activates narrow semantic fields, activating only dominant meanings, or meanings that are most relevant to the immediate context.

The novel approach that we take here is to attempt to explain how Beeman et al.'s (1994) fine-coarse model can account for the findings that (a) an *unrelated* stream of words presented to the right-ear/LH suppresses false recall, and that (b) the intrusions produced when *unrelated* words are presented to the right-ear/LH are greater in output-dominance (Sörqvist et al., 2010). One possible explanation for these findings, that concerns false recalls, can be found in relation to how hemispheric differences in semantic activation influences selection of candidates for recall.

Semantic activation across the hemispheres is defined in terms of: speed, strength, and breadth. In the LH, semantic activation quickly focuses in on a narrow semantic field of strongly activated items relevant to the current task. In contrast, the pattern in the RH is more diffuse and weak, activating a broad semantic field of both more and less relevant related items. These different patterns of activation across the hemispheres (LH: quick, small, strong versus RH: slow, broad, weak), are likely to result in a different level of false recall. We expand on this point below.

LEFT HEMISPHERE PRESENTATION

Unattended related items

Strong activation quickly narrows down to focus on the cohort of relevant items (i.e., the TBR items). Some of the unattended related items would also fall within this narrow semantic field (**Figure 1**, Panel 1a). Connectivity between all these related items would likely boost levels of activation within the entire cohort. Furthermore, unattended items that are activated are likely to be

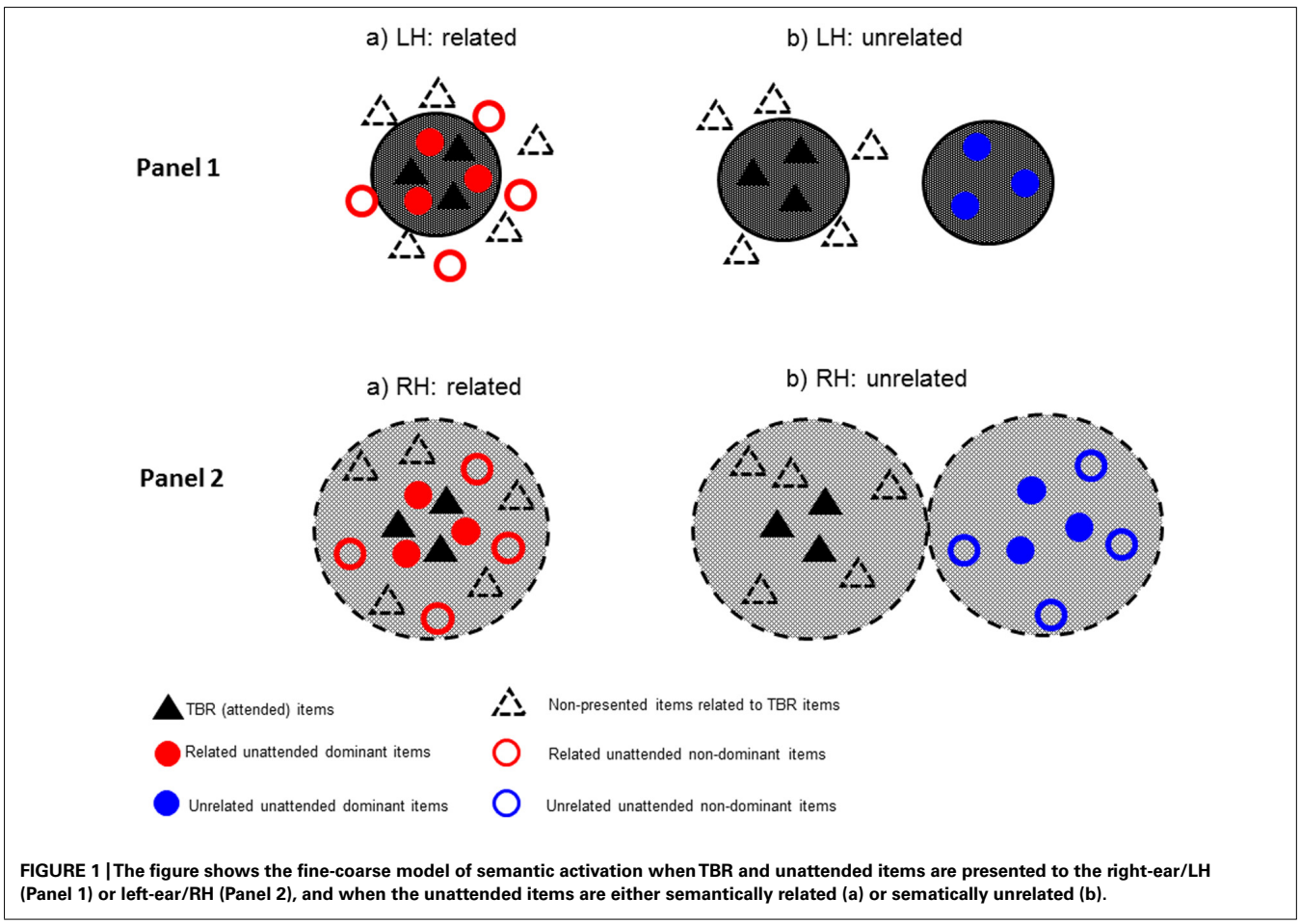


FIGURE 1 | The figure shows the fine-coarse model of semantic activation when TBR and unattended items are presented to the right-ear/LH (Panel 1) or left-ear/RH (Panel 2), and when the unattended items are either semantically related (a) or sematically unrelated (b).

the ones that are most closely related to the TBR items. In contrast, more distantly related items are likely to be outside this core semantic network and, thus, would not benefit from the strong activation and interconnectivity between items. This is likely to result in high levels of intrusion from closely related (dominant) items but with little interference from (and hence false recall of) distantly related (non-dominant) items.

Unattended unrelated items

The TBR and unattended unrelated items activate two separate semantic networks (**Figure 1**, Panel 1b). However, unlike the related condition, there would be no connectivity between TBR and unattended items and thus little interference. As with the unattended related items, false recall would likely be confined to dominant items closley related to the TBR items.

RIGHT HEMISPHERE PRESENTATION

Unattended related items

The RH weakly activates a broad, diffuse semantic network encompassing both TBR and unattended related items. Although intrusions are less likely than in the LH (due to weaker activation), the wide network of interconnected related items suggests that some unattended items are likely to reach a threshold where false recall is possible. Due to the broad semantic network activated, these intrusions would be equally likely from either closely related (dominant) or weakly related (non-dominant) items (**Figure 1**, Panel 2a). In addition, the diffuse activation makes it possible that related, but non-presented items, are also activated[1]. However, because of the strong competition from the mutally activating TBR and unattended items, non-presented items are unlikely to reach threshold for intrusion.

Unattended unrelated items

The TBR and unattended unrelated items activate two separate semantic networks (see **Figure 1** Panel 2b). Thus, unlike the unattended *related* items, the unattended *unrelated* items do not benefit from mutual activation via the TBR items. This would result in them having less chance of reaching threshold, as they receive no boost from interconnectivity with the TBR items. However, intrusions in the unattended unrelated condition would still be more likely in the RH than the LH, because the broad semantic network allows a greater connectivity between cohort members than in the LH, resulting in increased levels of activation for some items within the cohort. As in the unattended related condition, intrusions would be equally likely from either closely related (dominant) or weakly related (non-dominant) items. Finally, intrusions from non-presented items that are related to the TBR items may be slightly higher than in the unattended related condition, because they benefit from connnectivity with the TBR items, but do not suffer from additional competition from the unattended items.

EXTENSIONS AND PREDICTIONS OF THE MODEL

The fine-coarse model of hemispheric specialization supposes that the retrieval information from semantic memory (a process that underpins short-term memory for identity) will be vulnerable to disruption via meaningful speech presented to the right-ear/LH whereas the process of serial rehearsal (a process that underpins short-term memory for order) will be more impaired by acoustically variable sound presented to the left-ear/RH. Moreover, the model suggests that the ways in which background speech promotes false recall will depend on the semantic relation between targets and distracters and the dominance of the distracters. In general, the empirical findings presented here are consistent with the fine-coarse model.

The concept of hemispheric asymmetry in processing suggested by the fine-coarse model can be theoretically useful in informing the debate between interference-by-process (Jones and Tremblay, 2000; Marsh et al., 2009) and interference-by-content (Salamé and Baddeley, 1982, 1986; Neath, 2000) accounts of auditory distraction within short-term memory. The findings reviewed here are at odds with the interference-by-content approach whereby the irrelevant sound effect is viewed as a function of the similarity in identity between the TBR and irrelevant items. In contrast, the findings with by-ear presentation harmonize with the more dynamic interference-by-process account according to which the type of distraction that takes place (item or order based distraction) does not depend on the materials of the focal task but on the nature of the cognitive operations that are carried out to process that material. Here, we outline ways in which the fine-coarse model can be used to further explore this distinction between item and order based distraction.

FREE RECALL

One way to test the predictions of the fine-coarse model, as outlined, is through manipulating the output-dominance of the unrelated speech within free recall. Low output-dominant items that are weakly representative of their category should result in more activation – and hence promote more false recalls – when presented to the left-ear/RH in comparison with presentation to the right-ear/LH. A smaller by-ear effect should be found for the presentation of unrelated speech that conveys high output-dominant category members.

SERIAL RECALL

As noted, similarity in item identity between target and distracters can play a role in disruption of serial recall (Hughes and Jones, 2005). This can be further explored through manipulating the size of the TBR item set. For example, letters come from a wider set (26 in English) than digits (0–9) and thus the burden on item memory can be greater with letters. By-ear presentation could yield some clues as to whether some variants of the serial recall task simply tap into item-based effects. Specifically, the role of the RH (and therefore the left-ear disadvantage) should be much reduced (and possibly even turn into a right-ear disadvantage) when the serial recall task comprises a larger set (e.g., 8 of 26 items presented on any given trial). A further extension along these lines would be to investigate the role of individual differences. Individual differences in working memory capacity are unrelated to the magnitude of the changing-state effect (Sörqvist et al., 2013), but related to the ability to resist attention capture (Sörqvist, 2010) and to semantic effects (Beaman, 2004). As there are also substantial individual differences in ear-advantages (Hugdahl, 2000), perhaps the role

[1]In contrast, in the LH it is unlikely that non-presented items would be activated due to the narrow semantic field activated (see in **Figure 1** Panel 1).

for item-based disruption in the context of serial memory can be further explored by analyzing the relation between working memory capacity (WMC) and ear-disadvantages. Indeed, Beaman et al. (2007) suppose that WMC is associated with the capability to modify the activity or output from lexico-semantic analysis in the left superior temporal gyrus (STG).

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Response inhibition is modulated by functional cerebral asymmetries for facial expression perception

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The efficacy of executive functions is critically modulated by information processing in earlier cognitive stages. For example, initial processing of verbal stimuli in the language-dominant left-hemisphere leads to more efficient response inhibition than initial processing of verbal stimuli in the non-dominant right hemisphere. However, it is unclear whether this organizational principle is specific for the language system, or a general principle that also applies to other types of lateralized cognition. To answer this question, we investigated the neurophysiological correlates of early attentional processes, facial expression perception and response inhibition during tachistoscopic presentation of facial "Go" and "Nogo" stimuli in the left and the right visual field (RVF). Participants committed fewer false alarms after Nogo-stimulus presentation in the left compared to the RVF. This right-hemispheric asymmetry on the behavioral level was also reflected in the neurophysiological correlates of face perception, specifically in a right-sided asymmetry in the N170 amplitude. Moreover, the right-hemispheric dominance for facial expression processing also affected event-related potentials typically related to response inhibition, namely the Nogo-N2 and Nogo-P3. These findings show that an effect of hemispheric asymmetries in early information processing on the efficacy of higher cognitive functions is not limited to left-hemispheric language functions, but can be generalized to predominantly right-hemispheric functions.

Keywords: executive functions, Go/Nogo task, EEG, ERP, laterality, lateralization, Nogo-N2, Nogo-P3

INTRODUCTION

Intentional response inhibition is an executive control mechanism that is mainly regulated by the prefrontal cortex (e.g., Chikazoe, 2010). A commonly used method to experimentally assess this cognitive function is the Go/Nogo task in which participants have to perform a simple motor action (e.g., pressing a key on a PC keyboard) in response to one type of stimulus (Go), while they have to refrain from responding when the other type of stimulus (Nogo) is presented (e.g., Beste et al., 2010, 2013). One important factor modulating performance in Go/Nogo tasks is bottom-up information processing of the used stimuli (Knudsen, 2007), and it has been shown that hemispheric asymmetries for the used stimulus material affect the efficacy of response inhibition. For instance, Ocklenburg et al. (2011) tachistoscopically presented verbal "Go" and "Nogo" stimuli in the left and the right visual field (RVF) and reported that participants committed fewer false alarms when reacting to verbal Nogo-stimuli presented in the RVF than to stimuli presented in the left visual field (LVF), reflecting the well-known left-hemispheric dominance for processing of verbal stimuli (Hugdahl, 2000; Corballis, 2012; Hirnstein et al., 2012; Ocklenburg et al., 2012; Bless et al., 2013; Cai et al., 2013; Ocklenburg et al., 2013). Thus, initial stimulus representation in the non-dominant hemisphere seems to be leading to a less efficient inhibition process, an idea that was also supported by another divided visual field Go/Nogo study with verbal stimuli (Measso and Zaidel, 1990). However, it is unclear whether this effect is specific for the language system or a general principle that also applies to other types of lateralized cognition. Therefore, it was the aim of the present study to investigate whether the efficacy of response inhibition processes is also modulated by a typical right-sided functional asymmetry, the well-known right-hemispheric dominance for face processing (Levine et al., 1988; Rossion et al., 2003; Dien, 2009; Sung et al., 2011; Gainotti, 2013). To this end, we recorded event-related potentials (ERP's) during tachistoscopic presentation of facial "Go" and "Nogo" stimuli in the LVF and RVF.

The earliest ERP component that was assessed was the P1, a positive component with a peak between 80 to 120 ms after stimulus presentation (Proverbio et al., 2012) which is centered over the occipital cortex (electrodes O1 and O2). The P1 is the earliest endogenous visual ERP component and is reliably elicited in response to visual stimuli (Taylor, 2002; de Haan et al., 2003). It has been shown to be modulated by a number of factors, including stimulus characteristics and attentional processes (Herrmann and Knight, 2001; Herrmann et al., 2005; Beste et al., 2008; Martin et al., 2008; Wild-Wall et al., 2012). Interestingly, the P1 has been suggested to reflect early face processing (Itier and Taylor, 2002) and it has been found that the P1 is shorter to faces than inverted faces (Taylor, 2002) and that for central stimulus presentation, P1 amplitudes are more positive after presentation of stimuli showing make-up resembling a human face compared to animal-like make-up (Luo et al., 2013). However, there are also studies that did not

find any effect of faces compared to non-face visual patterns on the P1 (e.g., see Rossion et al., 1999). Findings regarding lateralization of the P1 are ambiguous, with some work reporting no significant side effects (Herrmann et al., 2005) while a recent study by Proverbio et al. (2012) reported that the P1 in a face-sex categorization task was left lateralized in women and bilateral in men.

The second early ERP component that was assessed was the N170 (Bentin et al., 1996; Itier et al., 2006, 2011). The N170 is a negative component which peaks about 130 to 170 ms after stimulus presentation, is usually centered over the occipito-temporal cortex (Bentin et al., 1996; Eimer, 2000; Rossion and Gauthier, 2002; Rossion et al., 2003; Bieniek et al., 2013). For central stimulus presentation, N170 amplitudes are more negative after presentation of face-like make-up stimuli compared to animal-like make-up stimuli (Luo et al., 2013). Functionally, it is thought to reflect structural encoding of faces (Herrmann et al., 2005). Rossion et al. (2003) reported right lateralization of the N170 for faces. In contrast, it was bilateral for cars and left-lateralized for words. In accordance with these findings, right lateralization of the N170 was also reported by several other studies (e.g., Bentin et al., 1996; Balconi and Lucchiari, 2005; Maurer et al., 2008; Mercure et al., 2008; but see: Proverbio et al., 2010).

In addition to these early ERP components, it is also of interest to assess whether the neurophysiological correlates of response inhibition, such as the Nogo-N2 and Nogo-P3, are modulated by tachistoscopic presentation of facial Go and Nogo stimuli. This is particularly interesting in order to elucidate whether lateralized processing in perceptual and early attentional cognitive processes affect higher cognitive functions such as executive control. The Nogo-N2 is a negative component that is thought to be related to either pre-motor inhibition (Falkenstein et al., 1999) or response conflict (Nieuwenhuis et al., 2003). Ocklenburg et al. (2011) could show that the N2 is lateralized when verbal "Go" and "Nogo" stimuli are presented tachistoscopically in the left and the RVF, so that initial stimulus processing is limited to one hemisphere. In accordance with the conflict hypothesis by Nieuwenhuis et al. (2003), the Nogo-N2 was stronger in response to Nogo-stimuli presented in the LVF. Thus, initial stimulus processing by the subdominant hemisphere leads to a stronger response conflict than initial processing by the dominant hemisphere, even if the inhibition process itself is driven by bilateral prefrontal networks. Apart from the Nogo-N2, the Nogo-P3 has also been related to response inhibition. The Nogo-P3 is a late positive component that has been linked to the evaluation of successful inhibition (Band and van Boxtel, 1999; Roche et al., 2005; Sehlmeyer et al., 2010; Smith et al., 2010, 2013; Beste et al., 2011a). For the Nogo-P3, Ocklenburg et al. (2011) did not observe as clear an asymmetry effect as for the Nogo-N2, but there was a non-significant trend for lateralization on Nogo-trials only.

Based on these findings, we hypothesize that in our task, participants should commit fewer false alarms on Nogo-trials after stimulus presentation in the LVF. This behavioral performance asymmetry should be accompanied by electrophysiological asymmetries on the level of the P1, N170, N2 and possibly P3.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-eight neurologically healthy volunteers (17 female, 11 male) with a mean age of 24.35 years (range: 21–32 years) participated in the present study. Handedness was assessed using the German version of the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). All participants were right-handed according to the results of EHI (mean laterality quotient 91.5; range 56–100). All participants gave written informed consent and were treated in accordance with the declaration of Helsinki. The study was approved by the ethics committee of the Faculty of Psychology, Ruhr-University Bochum, Germany.

EXPERIMENTAL PARADIGM

A Go/Nogo task was used to measure response inhibition to face stimuli that were presented tachistoscopically on a 17″ CRT computer monitor. Subjects had to react to "Go"-stimuli by pressing a key on a custom-made reaction-pad, and to refrain from pressing the key after a "Nogo"-stimulus was presented. The stimuli were two morphed male faces taken from the BESST (Bochum Emotional Stimulus Set; Thoma et al., 2012): a friendly and an angry face. To control for possible valence effects of the emotional faces, each participant completed two blocks in randomized order, one block in which the friendly face was the "Go"-stimulus and the angry face was the "Nogo"-stimulus and another block in which the angry face was the "Go"-stimulus and the friendly face was the "Nogo"-stimulus. On half of the trials within each experimental block, subjects responded toward the "GO" stimulus with the index finger of their right hand, and on the other half they responded with their left index finger toward the "GO" stimulus, in randomized order. Overall, the task consisted of 2560 trials (1280 per block), with 1792 trials being "Go"-trials (70%) and 768 trials being "Nogo" trials (30%). On half of the trials, stimuli were presented in the LVF, in the other half in the RVF, in randomized order. At the beginning of the experiment, participants were instructed to place the head on a chin rest placed at a distance of 57 cm from the monitor. Accordingly, 1 cm on the screen represented 1° of visual angle. Stimuli had a maximum width of 3° visual angle (from ear to ear) and a maximum height of 5° visual angle (from the neck to the top of the head.). Subjects were instructed to fixate a black fixation cross that was presented in the middle of the screen throughout the experiment. Each trial started with tachistoscopic presentation of the stimulus for 185 ms. Afterward, the central fixation cross was presented for 365 ms (Ocklenburg et al., 2011). The inter-trial interval was randomized between 750 and 950 ms. Only the central fixation cross was presented during this interval.

EEG RECORDING AND ANALYSIS

EEG data were recorded from 65 active Ag–AgCl electrodes at standard scalp positions against a reference electrode located at FCz. Data were recorded with a sampling rate of 1000 Hz, and down-sampled off-line to 128 Hz. All electrode impedances were kept below 5 kΩ. The data was band-pass filtered (0.5–20 Hz) offline before further data processing and then visually inspected to remove technical artifacts. Horizontal and vertical

eye movements as well as pulse artifacts were then corrected using an independent component analysis (ICA; Infomax algorithm) applied to the un-epoched data set. In the epoched data, automated artifact rejection procedures with the following rejection criteria were applied: maximum voltage steps of more than 50 μV/ms, maximal value differences of 200 μV in a 200 ms interval, or activity below 0.1 μV. To achieve a reference-free evaluation, peak, and latency analyses were performed after calculation of current source density (CSD) of the signals (Perrin et al., 1989). For statistical analysis, amplitudes were quantified relative to a baseline covering 200 ms before stimulus presentation until stimulus onset. Averaging was locked at the time point of "Go"- or "Nogo"-stimulus presentation and analysis epochs had a length of 1500 ms (from 200 ms before stimulus presentation until 1300 ms after stimulus presentation). Subsequent to averaging, P1, N170, and N2 amplitudes in "Go"- and "Nogo"-trials were calculated relative to baseline using only trials on which participants had reacted correctly. P3 amplitudes were calculated relative to N2 amplitudes. For each ERP component, the local maximum (for positive components) or minimum (for negative components) within a given time window (P1: 50–150 ms after stimulus presentation; N170: 100–200 ms; N2: 200–400 ms; P3: 250–550 ms) was determined. This was done using a semi-automated search function implemented in the analysis software. The results of the automated search were then visually inspected and corrected of necessary. For the P1, amplitudes and latencies were quantified at the standard positions O1 and O2, while for the N170, amplitudes and latencies were quantified at electrodes CP5 and CP6. For the Nogo-N2 and Nogo-P3, amplitudes and latencies were quantified at the standard position FCz.

STATISTICAL ANALYSIS

The behavioral data (i.e., rate of false alarms on Nogo trials as well as misses and reaction times on Go-trials) were analyzed using paired samples t-tests to compare performance after stimulus presentation in the LVF and RVF. P1 and N170 data were analyzed using repeated measures analyses of variance (ANOVAs) with the within-subjects factors electrode (P1: O1 and O2; N170: CP5 and CP6), condition (Go, Nogo), and visual half-field (RVF, LVF). N2 and P3 data were analyzed using repeated measures ANOVAs with the within-subjects factors condition (Go, Nogo) and visual half-field (RVF, LVF). When appropriate, the degrees of freedom were adjusted using Greenhouse–Geisser correction. The *p*-levels for *post hoc* testing were adjusted using Bonferroni correction. Effect sizes are provided as the proportion of variance accounted for (partial η^2). As a measure of variability, the standard error of the mean (SEM) was used. All statistical analyses were conducted using IBM SPSS Statistics 20.

RESULTS

BEHAVIORAL DATA

In Nogo-trials, the false alarm rate was higher for stimuli that were presented in the RVF (29.82% ± 3.77) than for stimuli that were presented in the LVF (25.69% ± 3.12; $t_{(27)} = 2.39$; $p < 0.05$). In contrast, no visual field difference was observed for the number of misses on Go-trials (RVF: 8.43% ± 2.16; LVF: 8.43% ± 2.29; $t_{(27)} = 0.01$; $p = 0.99$) or reaction time on correct Go-trials (RVF: 472.09 ms ± 11.19; LVF: 468.11 ms ± 11.22; $t_{(27)} = -1.14$; $p = 0.27$).

NEUROPHYSIOLOGICAL DATA

P1

For P1 amplitudes (see **Figure 1**), the ANOVA revealed a main effect of electrode [$F_{(1,27)} = 4.42$; $p < 0.05$; partial $\eta^2 = 0.14$], indicating a more positive amplitude of the P1 at the left-sided electrode O1 (24.47 ± 2.94) compared to the right-sided electrode O2 (18.86 ± 3.07). In addition, a significant interaction visual half-field × electrode [$F_{(1,27)} = 4.38$; $p < 0.05$; partial $\eta^2 = 0.14$] indicated that after stimulus presentation in the RVF, the P1 was more positive at the left-sided electrode O1 (27.71 ± 4.08) than at the right-sided electrode O2 (16.01 ± 2.59; Bonferroni corrected

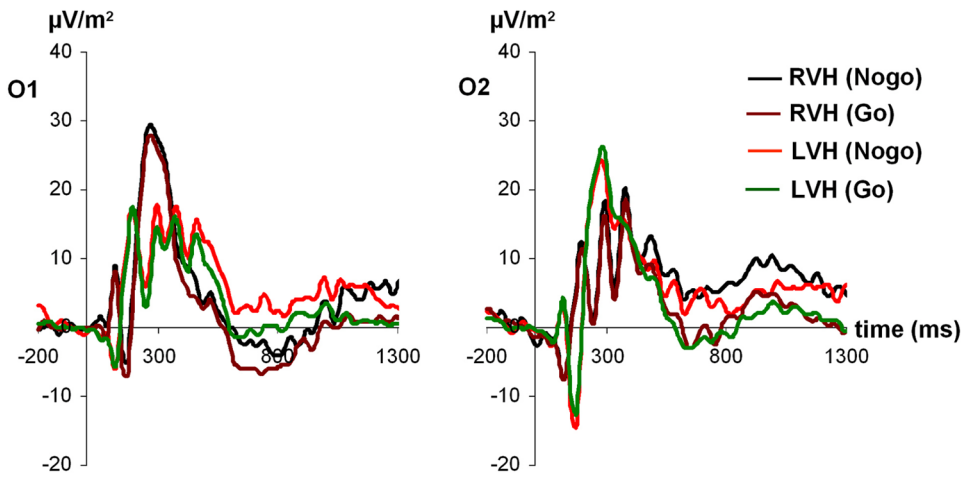


FIGURE 1 | Time course of ERP components at electrodes O1 and O2 in the Go and Nogo condition after stimulus presentation in the left and right visual field. Time point 0 indicates the point of Go- or Nogo-stimulus presentation.

post hoc test: $p < 0.01$). In contrast, after stimulus presentation in the LVF, no amplitude difference between the two electrodes was observed (O1: 21.22 ± 2.62; O2: 21.71 ± 4.12; Bonferroni corrected *post hoc* test: $p = 1.00$). Moreover, a significant interaction visual half-field × condition emerged [$F_{(1,27)} = 4.35$; $p < 0.05$; partial $\eta^2 = 0.14$], indicating a visual half-field difference between Go- and Nogo-trials, but both *post hoc* tests failed to reach significance, indicating a rather weak effect (Go-trials: LVF: 21.40 ± 2.67; RVF: 20.40 ± 3.05; Bonferroni corrected *post hoc* test: $p = 1.00$; Nogo-trials: LVF: 21.53 ± 2.86; RVF: 23.32 ± 2.88; Bonferroni corrected *post hoc* test: $p = 0.74$). All other main effects and interactions failed to reach significance (all $p > 0.11$).

For P1 latencies, only the visual half-field × condition interaction reached significance [$F_{(1,27)} = 4.37$; $p < 0.05$; partial $\eta^2 = 0.14$], indicating a trend toward a smaller P1 latency on Nogo-trials after stimulus presentation in the LVF (126.27 ms ± 9.20) compared to the RVF (RVF: 139.23 ms ± 8.79; Bonferroni corrected *post hoc* test: $p = 0.33$; Go-trials: LVF: 140.49 ms ± 9.96; RVF: 132.95 ms ± 10.30; Bonferroni corrected *post hoc* test: $p = 0.80$). However, since both *post hoc* tests failed to reach significance, this effect seems to be rather weak. Moreover, a trend toward a visual half-field × electrode interaction emerged [$F_{(1,27)} = 3.46$; $p = 0.07$; partial $\eta^2 = 0.11$]. All other main effects and interactions failed to reach significance (all $p > 0.11$).

N170

For N170 amplitudes (see **Figure 2**), the ANOVA revealed a significant main effect of condition [$F_{(1,27)} = 4.48$; $p < 0.05$; partial $\eta^2 = 0.14$], indicating that the N170 was more negative on Nogo-trials (−15.76 ± 1.20) compared to Go-trials (−14.34 ± 1.12). Moreover, an interaction visual half-field × electrode emerged [$F_{(1,27)} = 17.08$; $p < 0.001$; partial $\eta^2 = 0.39$], indicating that after presentation of a face in the LVF, the N170 was more negative at the right-sided electrode CP6 [−19.03 ± 1.87] than at the left-sided electrode CP5 (−12.68 ± 1.56, Bonferroni-corrected *post hoc* test: $p < 0.05$]. For presentation of a face in the RVF, a trend toward the opposite direction was observed (CP5: −16.05 ± 1.71; CP6: −12.45 ± 1.35), but the *post hoc* test failed to reach significance ($p = 0.19$). In addition, a trend toward a condition × visual half-field × electrode emerged [$F_{(1,27)} = 2.88$; $p = 0.10$; partial $\eta^2 = 0.10$]. All other main effects and interactions failed to reach significance (all $p > 0.13$). The visual half-field × electrode interaction also reached significance for N170 latency [$F_{(1,27)} = 6.25$; $p < 0.05$; partial $\eta^2 = 0.19$]. After presentation of a face in the LVF, the N170 had a longer latency at the right-sided electrode CP6 (173.55 ms ± 5.14) than at the left-sided electrode CP5 (147.18 ms ± 9.48, Bonferroni-corrected *post hoc* test: $p < 0.05$). For presentation of a face in the RVF, no significant difference between electrodes was observed (CP5: 173.97 ms ± 9.13; CP6: 165.46 ms ± 8.08; Bonferroni-corrected *post hoc* test: $p = 0.80$). All other main effects and interactions failed to reach significance (all $p > 0.11$).

N2 and P3

For N2 amplitudes (see **Figure 3**), the ANOVA revealed a significant main effect of condition [$F_{(1,27)} = 6.45$; $p < 0.05$; partial $\eta^2 = 0.19$), indicating that the N2 was more negative on Nogo-trials (−14.06 ± 1.71) than on Go-trials (−10.57 ± 1.36). Moreover, a significant main effect of visual half-field emerged [$F_{(1,27)} = 4.91$; $p < 0.05$; partial $\eta^2 = 0.15$], indicating that the N2 was more negative after stimulus presentation in the RVF (−14.25 ± 1.91) than after stimulus presentation in the LVF (−10.37 ± 1.32). The visual half-field × condition interaction failed to reach significance ($p = 0.36$). For N2 latencies, all effects failed to reach significance (all $p > 0.11$).

Due to N2 amplitude differences, P3 amplitudes were not determined peak-to-baseline but peak-to-peak, with the N2 serving as baseline. Only the main effect of condition reached significance [$F_{(1,27)} = 13.99$; $p < 0.05$; partial $\eta^2 = 0.34$], indicating that Δ was larger on Nogo-trials (23.50 ± 2.43) than on Go-trials (15.21 ± 1.96). All other effects failed to reach significance (all $p > 0.20$).

For P3 latencies, the main effect of visual half-field reached significance [$F_{(1,27)} = 6.07$; $p < 0.05$; partial $\eta^2 = 0.18$], indicating that the P3 had a longer latency after stimulus presentation in

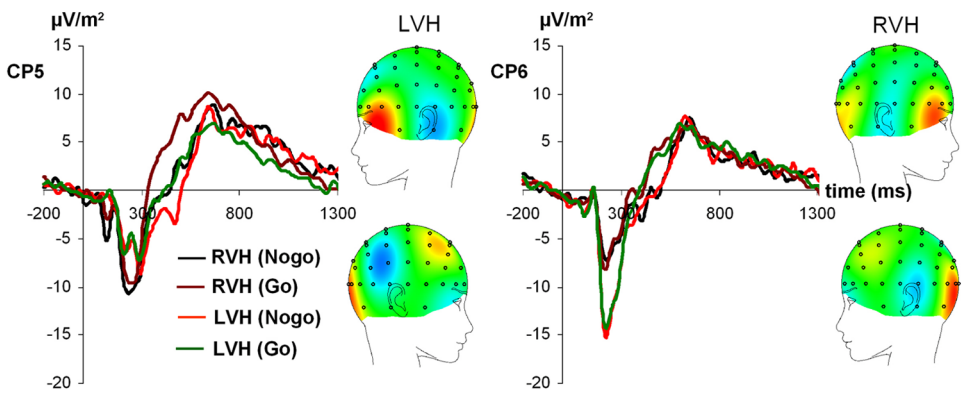


FIGURE 2 | Time course of ERP components at electrodes CP5 and CP6 in the Go and Nogo condition after stimulus presentation in the left and right visual field. Time point 0 indicates the point of Go- or Nogo-stimulus presentation.

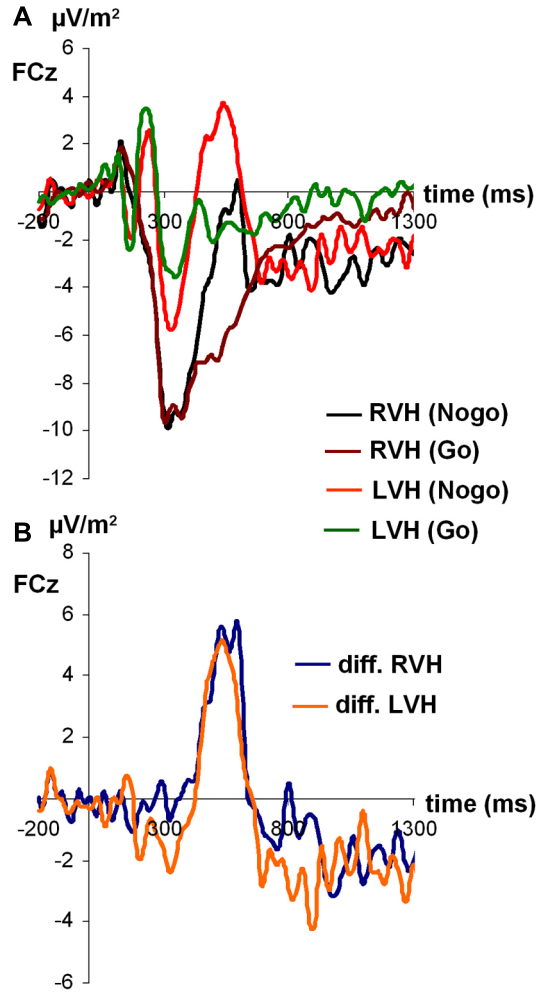


FIGURE 3 | (A) Time course of ERP components at electrodes FCz in the Go and Nogo condition after stimulus presentation in the left and right visual field. **(B)** Time course of ERP components at electrodes FCz as difference between Go and Nogo condition for the left and right visual field. Time point 0 indicates the point of Go- or Nogo-stimulus presentation.

the RVF (492.89 ms ± 20.11) than after stimulus presentation in the LVF (410.30 ms ± 27.31). This effect was modulated by condition, as indicated by a significant interaction visual half-field × condition [$F_{(1,27)} = 5.99$; $p < 0.05$; partial $\eta^2 = 0.18$]. Interestingly, the visual half-field difference reached significance only on Nogo-trials (LVF: 399.28 ± 31.14; RVF: 551.89 ± 26.38; Bonferroni-corrected *post hoc* test: $p < 0.01$), but not on Go-trials (LVF: 421.32 ± 38.99; RVF: 433.87 ± 33.59; Bonferroni-corrected *post hoc* test: $p = 1.00$). The main effect of condition failed to reach significance ($p = 0.18$).

Since there is some controversy surrounding the use of the peak amplitude as a measure for the P3 (Luck, 2005), we also calculated the mean amplitude from 400 to 500 ms after stimulus presentation as an alternative measure for the P3. As for the peak amplitude, the main effect of condition reached significance [$F_{(1,27)} = 10.95$; $p < 0.01$; partial $\eta^2 = 0.29$], indicating the P3 was more positive on Nogo-trials (1.21 ± 2.32) than on Go-trials (−4.18 ± 1.51). Moreover, the main effect of visual half-field reached significance [$F_{(1,27)} = 6.90$; $p < 0.05$; partial $\eta^2 = 0.20$], indicating a more positive P3 after stimulus presentation in the LVF (1.71 ± 1.96) than after stimulus presentation in the RVH (−4,68 ± 2.33). The interaction failed to reach significance ($p = 0.09$).

DISCUSSION

Functional cerebral asymmetries have been shown to modulate the efficacy of executive functions (Measso and Zaidel, 1990; Ocklenburg et al., 2013). While previous studies investigated how the left-hemispheric language dominance affects these prefrontally mediated cognitive functions, the present study was aimed at answering the question how executive functions are modulated by the right-hemispheric dominance for face processing. To this end, we recorded ERPs on a tachistoscopic version of the classic Go/Nogo task in which faces were presented in the left and RVF.

Behaviorally, participants committed fewer false alarms on Nogo-trials after stimulus presentation in the LVF. In line with the results of several earlier studies using the divided visual field technique with face stimuli (Leehey and Cahn, 1979; Young and Bion, 1981; Levine and Koch-Weser, 1982; Young, 1984; Young et al., 1985;Gainotti, 2013), this finding indicates greater efficacy of the right hemisphere for facial expression perception. In contrast, no hemispheric asymmetries were observed for accuracy or reaction times on Go-trials, which may be attributed to low task demands in the Go-condition possibly resulting in a ceiling effect. Moreover, this finding is also in line with the behavioral results of earlier studies that used divided visual fields versions of the Go/Nogo Task with verbal stimuli. These studies found that response inhibition is more efficient when initial stimulus processing is performed by the dominant hemisphere (Measso and Zaidel, 1990; Ocklenburg et al., 2013). Our findings indicate that this connection between functional hemispheric asymmetries and executive functions is not limited to left-hemispheric language function, but can also be observed for right-hemispheric functions.

In the ERP data, asymmetries were observed for various components in different cognitive processing stages. In accordance with the results of Proverbio et al. (2012) for female participants, we found left lateralization of the P1 after stimulus presentation in the RVF. Stimulus presentation in the LVF, however, did not lead to any asymmetry effects. This finding further supports the assumption of Proverbio et al. (2012) that for some types of face-processing tasks at least some left-hemispheric functions are necessary. Specifically, Proverbio et al. (2012) argued that facial tasks which require a high amount of local feature analyses may lead to left-lateralization of the P1 because local visual analyses are known to activate more left-hemispheric networks than global visual analyses (e.g., Hellige, 1996; Yovel et al., 2001). Since we used emotional faces in the present study, which differed mainly with regard to those parts of the face that communicate emotions (e.g., mouth, eyes, and eye-brows), one could speculate that participants partly relied on local visual analysis of these face features to react correctly, ultimately leading to the observed left-lateralization of the P1.

For the N170, the largest negative amplitude was observed at the right-sided electrode CP6 after stimulus presentation in the LVF.

Moreover, only after stimulus presentation in the LVF (and thus initial stimulus processing in the dominant right hemisphere), did a significant amplitude difference between right- and left-sided electrodes emerge. Here, the N170 had a more negative amplitude at the right compared to the left electrode site. After stimulus presentation in the RVF (and thus initial stimulus processing in the non-dominant left hemisphere), no electrode difference was observed. Thus, in line with other studies reporting right-sided lateralization of the N170 (e.g., Bentin et al., 1996; Rossion et al., 2003; Balconi and Lucchiari, 2005; Maurer et al., 2008; Mercure et al., 2008), our results further support the assumption that the N170 is specifically driven by right-hemispheric brain areas, e.g., the fusiform gyrus or the superior temporal sulcus (Schweinberger et al., 2002; Shibata et al., 2002; Dalrymple et al., 2011). In contrast to the clear right-lateralization of the N170 amplitudes, the N170 had a longer latency over the right than over the left hemisphere when a stimulus was presented in the LVF. Interestingly, a similar finding has also been reported by Proverbio et al. (2012) for central stimulus presentation. In line with the discussion of the P1 findings, this result could be indicative of a need for left-hemispheric processing for certain aspects of our task, e.g., a local feature analysis of the emotional content of the face.

In general, the Nogo-N2 and Nogo-P3 data indicated that our tachistoscopic divided visual field version of the Go/Nogo task worked as intended, since we observed the typical pattern of results for these components. In accordance with previous studies utilizing this paradigm with central stimulus presentation (Beste et al., 2011b; Smith and Douglas, 2011), the Nogo-N2 was more negative after Nogo- than after Go-stimuli, and the Nogo-P3 was more positive after Nogo- than after Go-stimuli. For central stimulus presentation, both the Nogo-N2 and the Nogo-P3 are focused over fronto-central electrode sites (Falkenstein, 2006; Beste et al., 2010) and their generators have been localized mainly in the orbitofrontal cortex (Beste et al., 2010), with some authors reporting a right-shifted topography (Falkenstein, 2006), the inferior frontal cortex (Aron et al., 2004), and the anterior cingulate cortex (Nieuwenhuis et al., 2003).

In contrast to Ocklenburg et al. (2011) who found that the Nogo-N2 was stronger in response to Nogo-stimuli initially processed by the subdominant hemisphere, we found that for facial stimuli, the Nogo-N2 was more negative after initial processing in the subdominant hemisphere, regardless of condition. This difference between the two studies could possible indicate a response conflict in the Go-condition in the present study. For example, the higher stimulus complexity in the present paradigm could have rendered it more difficult for participants to react correctly on both Go and Nogo-trials than in the study by Ocklenburg et al. (2011). This assumption is supported by false alarm rates being overall higher in the present study than in studies using verbal stimuli (present study: RVF: 29.82%; LVF: 25.69%; Measso and Zaidel, 1990: RVF: 11.8%; LVF: 20.1%; Ocklenburg et al., 2011: RVF: 12.9%; LVF: 16.4%). Moreover, the miss rate for go-stimuli was around 8% in the present study, indicating that even when being asked to execute the predominant go-reaction, participants sometimes experienced problems to perform correctly. In addition to the generally higher complexity of the facial stimuli used in the present study, verbal stimuli typically used in Go/Nogo tasks (e.g., the words "Press" and "Stop") are usually highly overlearned, since they have been associated with performing a reaction or refraining from doing so in everyday life. In contrast, in the present study, participants had to learn which stimuli represented a Go-signal or Nogo-signal during the experiment.

In addition to the Nogo-N2 results, we also observed an effect of functional cerebral asymmetries for facial expression perception on Nogo-P3 latencies. On Nogo-, but not on Go-trials, the P3 had a longer latency if initial stimulus processing was conducted by the non-dominant left hemisphere. Thus, initial stimulus processing by the dominant right hemisphere leads to faster evaluation of the inhibition process (Band and van Boxtel, 1999; Roche et al., 2005; Smith et al., 2010, 2013).

There are a few methodological considerations that have to be taken into account when interpreting the present ERP results. First of all, the P1 effects seem to be rather weak, since the half-field × condition interaction reached significance for both amplitudes and latencies, but both *post hoc* tests failed to reach significance for both variables after Bonferroni correction. This potential issue might be due to the fact that the P1 is not specifically elicited by perception of faces, but by perception of visual stimuli in general (Taylor, 2002; de Haan et al., 2003). To address this potential lack of statistical power to reliably detect P1 asymmetry effects, future studies investigating this topic should test larger samples and use a higher number of trials than the present work. One methodological consideration that has to be taken into account when interpreting the N2 and P3 results is the fact that it is not clear to what extent results obtained in a paradigm with lateralized stimulus presentation allow to draw conclusions about the impact of hemispheric asymmetries when stimuli are presented in the center of the visual field. For example, ERP studies in the field of hemispheric asymmetries in global vs. local processing demonstrate that central vs. lateralized presentation could affect the occurrence of hemispheric asymmetries: while all ERP studies with central stimulus presentation reported hemispheric asymmetries, some studies with laterally presented stimuli failed to replicate this finding (see Volberg and Hübner, 2004, for an overview). Thus, it would be interesting for futures studies investigating the impact of lateralization on executive functions to include a condition with central stimulus presentation in addition to stimulus presentation in the LVH and RVF. In regard to the present results, this would allow to differentiate hemispheric asymmetries for centrally presented faces (e.g., as reported by Rossion et al., 2003, for the N170) from hemispheric asymmetries following laterally presented stimuli.

Taken together, the present findings show that hemispheric asymmetries in information processing as reflected by early ERP components such as the N170 affect behavioral performance indicators as well as neurophysiological correlates of higher cognitive functions. In principle, initial stimulus processing by the dominant hemisphere leads to more efficient execution of subsequent cognitive tasks, even if task-related ERP components are mediated by bilateral neuronal networks, as is the case for Nogo-N2 and Nogo-P3 (Ocklenburg et al., 2011). This principle is not limited to left-hemispheric language functions, as has been suggested by previous studies, but can also be applied to predominantly right-hemispheric functions. However, it is obvious that the results

for facial stimuli do not completely mirror the results for verbal stimuli. Thus, the present findings also indicate that it is important to consider both the specific neurobiological properties of the involved cognitive system as well as stimulus variables such as complexity when investigating the impact of functional cerebral asymmetries in information processing on higher cognitive systems.

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Differences between visual hemifields in identifying rapidly presented target stimuli: letters and digits, faces, and shapes

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The right hemisphere has been shown to play a dominant role in processing of visuo-spatial information. Recently, this role has been studied in the two-stream rapid serial visual presentation task. In this task, two alphanumerical targets are embedded in left and right simultaneous streams of rapidly changing letters. The second target (T2) is identified better in the left than in the right visual field. This difference has been interpreted as advantage of the right hemisphere (RH). However, a disadvantage of the left hemisphere (LH) could not be excluded so far. The LH, specialized for processing of verbal stimuli, might be overloaded due to constant input of letters from both visual fields. In the present study, this overload hypothesis was tested by reducing demands on verbal processing (Experiment 1), and by overloading the RH with non-verbal stimuli: faces (Experiment 2) and irregular shapes (Experiment 3). The left visual field advantage proved to be largely independent from the level of verbal load and from stimulus type. Therefore, although not entirely disproving the overload hypothesis, these results suggest as the most parsimonious explanation this asymmetry reflects a RH advantage, presumably in perceptual and attentional processing, rather than a LH disadvantage caused by verbal overload.

Keywords: RSVP, visual perception, hemispheric asymmetry, hemispheric specialization, lateralization, left visual-field advantage

INTRODUCTION

Spatio-temporal dynamics of visual information processing has been recently studied using a two-stream variant of the rapid serial visual presentation (RSVP) task (Shih, 2000; Holländer et al., 2005; Verleger et al., 2009, 2010, 2011; Akyürek et al., 2010; Śmigasiewicz et al., 2010). In this task, participants have to identify two consecutive targets, T1 (e.g., a red letter) and T2 (e.g., a black digit), embedded in either of two rapidly changing streams of successive distractors (e.g., black letters). The streams are presented in the left and right visual fields simultaneously, T1 is presented in the left or in the right stream, and T2 follows T1 with different lags either in the same or in the opposite stream. Identification of T1 is usually equally accurate in both streams, or slightly better in the right visual field (RVF) (Śmigasiewicz et al., 2010), which is consistent with left hemisphere (LH) specialization in processing of verbal or symbolic stimuli, like letters, words, and Arabic numbers (Dien, 2009; Dehaene and Cohen, 2011). In contrast, T2 is identified up to 30% better in the left visual field (LVF) than in the RVF (Holländer et al., 2005; Verleger et al., 2009, 2010, 2011; Śmigasiewicz et al., 2010) and is also rated to occur earlier in the LVF than in the RVF (Matthews et al., 2013). These findings are not only utterly contradictory to our subjective feeling of being equally aware of visual events in both hemifields, but also contrast with small VF effect sizes usually observed in behavioral studies of visuo-spatial processing. Typically, differences between VFs amount to around 10–20 ms in response time, or few percentage points in accuracy (see Hellige et al., 2010 for a review), and may not be easily replicable (Verfaellie et al., 1988; Evert et al., 2003; see also Hellige et al., 2010).

The mechanism underlying this prominent LVF advantage in two-stream RSVP has still remained undetermined. Although right hemisphere (RH) superiority for perceptual or attentional processes has been suggested as a possible explanation (Holländer et al., 2005; Verleger et al., 2009, 2011), this visual field asymmetry may actually result from LH disadvantage rather than from RH advantage (Hellige et al., 1979; Holländer et al., 2005; Verleger et al., 2010). In all previous two-stream RSVP studies alphanumerical verbal stimuli were used as targets and distractors, which stimuli have been shown to be processed more efficiently by the LH in most right-handed individuals (Pujol et al., 1999). According to the callosal relay model of functional hemispheric lateralization (Zaidel, 1983; Moscovitch, 1986), information that cannot be efficiently processed by one hemisphere due to lack of specialized systems is relayed to the more competent hemisphere through the corpus callosum. Imaging studies provided direct evidence for this model, showing that a left-lateralized linguistic neural network is strongly engaged by alphabetic stimuli, regardless of the input hemifield (Cohen et al., 2002). A recent electrophysiological study has shown that the transfer of verbal information from the LVF/RH to the LH begins already about 100 ms after stimulus onset, thereby suggesting that interhemispheric communication includes sharing of low level information

already at early stages of processing (Doron et al., 2012). In two-stream RSVP, the rapidly presented series of distractor letters have to be processed, at least to some degree, in search for targets. Therefore, the LH, responsible for processing of verbal stimuli (Dien, 2009; Dehaene and Cohen, 2011), might have to cope with constant input from both VFs simultaneously, and thus could be overloaded (Hellige et al., 1979; Verleger et al., 2010). The overload may disrupt the LH's ability to single out the second target from the two streams of letter distractors presented in rapid succession.

Several previous studies have shown that LH efficiency may be indeed compromised by increased demands for verbal processing. For instance, Hellige and colleagues (Hellige and Cox, 1976; Hellige, 1978; Hellige et al., 1979) demonstrated that a concurrent verbal memory task, which is supposed to tax the LH, impairs identification of laterally presented stimuli more in the RVF than in the LVF, and may even lead to a LVF advantage in tasks in which usually a RVF advantage is observed. It has also been argued that the LH should be more affected by Stroop interference than the RH, due to the lateralization of language-related processes (see MacLeod, 1991). Several studies with a lateralized Stroop task have suggested that this might hold true (Schmit and Davis, 1974; Franzon and Hugdahl, 1987; Weekes and Zaidel, 1996; Gier et al., 2010), although the alternative interpretation of the asymmetry as due to RH superiority in attentional control (like the usual interpretation of the two-stream RSVP asymmetry) is also plausible (Asanowicz et al., 2012). Another piece of evidence that seems to support the overload hypothesis comes from a two-stream RSVP study, which has shown that repetitive transcranial magnetic stimulation (rTMS) applied to the left parietal cortex increased, to some extent, the LVF advantage in T2 identification, whereas rTMS to the right hemisphere did not bring about any significant changes in the asymmetry (Verleger et al., 2010). The LH, as being supposedly more engaged during the task might have been more susceptible to applied disruption.

The present study aimed to further investigate whether the overload hypothesis can explain the LVF advantage in T2 identification in two-stream RSVP. Two approaches were applied to this end. First, the verbal processing demands of two-stream RSVP were diminished by reducing the distractor load, presenting only the distractors directly preceding and following T1 and T2, and by reducing the target load, requiring participants to identify T2 only, rather than T1 and T2 (Experiment 1). In line with the overload hypothesis, the LVF advantage—expected to be observed when using the standard two-stream RSVP procedure—should decrease or even disappear with this reduced load. This is because the LH, released from processing the letter distractors or the T1, should improve target identification up to a level comparable to the RH. The second approach relied on overloading the RH by presenting stimuli whose processing is supposed to be lateralized to the RH: faces (Experiment 2) and non-verbalizable irregular shapes (Experiment 3), instead of letters and digits. In line with the overload hypothesis, the RH load should reverse the hemispheric asymmetry, and thus produce an advantage of the RVF, rather than of the LVF. Alternatively, if due to some stimulus-independent factor, the LVF advantage will still be present despite these experimental manipulations.

EXPERIMENT 1

The aim of the first experiment was to test whether decreasing the verbal load will relieve the LH and improve T2 identification in the RVF. To this end, we reduced the load produced by distractors and the load produced by T1. In order to measure effects of the load produced by distractors, one group performed the standard version of the task with letters as distractors in the entire stream, while in the second group the number of distractor letters was reduced so that only the distractors preceding and following each target were presented. Similar variations of the number of stimuli have been used to manipulate load in various types of tasks (e.g., Hellige et al., 1979; Lavie et al., 2004). In order to reduce the load produced by identifying T1, a condition was included for both groups where T1 had to be ignored and only T2 had to be identified. This condition is also supposed to provide a baseline of visual-field asymmetry relatively unaffected by processing demands due to the requirement of identifying T1, like in Holländer et al. (2005) and many previous (one-stream) RSVP studies (see Nieuwenstein et al., 2009, for boundary conditions of T1 effects). Additionally, as in the previous two-stream RSVP experiments, the two targets were presented with different lags and counterbalanced across VFs to ensure uncertainty of T2 occurrence, to minimize potential effects of expectations and endogenous orienting of attention (Verleger et al., 2009). The overload hypothesis will be confirmed by decreased size of the LVF advantage in the conditions with fewer distractors and with one target only to identify, brought about by improved T2 identification in the RVF.

METHOD

Participants

Forty-four right-handed undergraduate students from Jagiellonian University participated in the experiment for course credit. Twenty-two of them (14 females, 8 males) took part in the experiment with the standard two-stream RSVP stimuli. Their mean age was 19.3 years ($SD = 1.0$), and their scores in the Edinburgh Handedness Inventory (Oldfield, 1971) were 87.7 ($SD = 11.3$). The other half of the sample participated in the experiment with fewer distractor stimuli. From the originally twenty-two participants in this group, two were excluded due to very low accuracy of T1 identification (below 30%), almost approaching chance level. In the remaining sample 12 were female and 8 male, their mean age was 20.2 ($SD = 1.7$), and their scores in the Edinburgh Handedness Inventory were 86.0 ($SD = 13.7$). All participants had normal or corrected-to-normal vision, reported normal color vision, and no history of neurological disorders.

Stimuli, apparatus, and procedure

Two-stream RSVP task. A sample stimulus sequence is illustrated in **Figure 1**. Two streams of black capital letters of the Latin alphabet were presented in the left and right visual field simultaneously on the white background of a 21′ screen. The frame rate of the monitor was 60 Hz, i.e., frame duration equaled 16.7 ms. Each pair of stimuli was displayed for a period of seven frames, 117 ms. Subsequent letters were displayed one after another without interstimulus intervals. Letter font was Helvetica 35, thus letters were

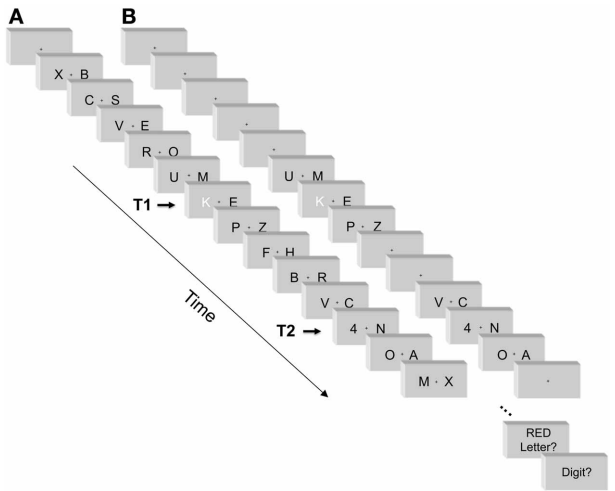


FIGURE 1 | An example of stimuli and sequence of events in a trial with standard number of distractors (A), and with reduced number of distractors (B). See Methods for details. Red color is replaced here by white.

11 mm high (0.8° visual angle). Their midpoints were 16 mm off screen center (1.1°), implying distances of their inner edges from screen center of around 11 mm (0.8°; varying between letters). Fixation was marked by a small dot positioned centrally on the screen (0.2° × 0.2°). In each trial, two target stimuli were displayed. The first target (T1) was a red capital letter (D, F, G, J, K, or L). The second target (T2) was a black digit (ranging from 1 to 6). The set size of six targets allows to decrease the number of correct lucky guesses, hence raises the reliability of the task. The remaining black letters displayed during the whole trial constituted the distractor set. The stimuli were presented via DMDX software (Forster and Forster, 2003).

Each trial started with a fixation period of 800 ms followed by a presentation of 12–20 subsequent pairs of stimuli. The fixation point was displayed throughout the whole trial. T1 was preceded by five, seven, or nine pairs of distractor letters, thus participants did not precisely know when it would occur. T2 followed T1 with lag 1 (no distractor letters between T1 and T2; stimulus onset asynchrony, SOA, equal to 117 ms), lag 3 (two pairs of distractors occurred between T1 and T2, SOA = 350 ms), or lag 5 (four pairs of distractors occurred between T1 and T2, SOA = 583 ms). T1 and T2 were presented in the left or right visual field with equal probability. In half of the trials, T2 occurred in the same VF as T1 ("same-side T2"), and in the other half in the opposite VF ("opposite-side T2"). Each trial ended with five letter pairs following T2. Therefore, trial length varied from 12 pairs of stimuli (when T1 came in the 6th letter pair and T1-T2 lag was 1) to 20 (when T1 came in the 10th letter pair and T1-T2 lag was 5). Target stimuli were randomly selected from the target sets. Distractor stimuli were randomly selected with replacement from the letter set, but consecutive and simultaneously presented distractors could not be identical.

Both for the group with normal number of distractors and the group with fewer distractors (2.1.2.2), there were two task conditions: dual and single-target. Both T1 and T2 had to be identified in the first condition, while T1 was ignored and only T2 had to be reported in the second condition. At the end of each trial, the fixation cross extinguished and a response screen appeared, displaying the six targets and the instruction to press the appropriate key on the computer keyboard indicating which red letter (T1) and black digit (T2) were displayed in the trial. In the single-target condition there was only the screen about T2. In the dual-target condition, the T2 response screen was preceded by the T1 response screen. Participants were informed that response times did not matter and that some responses had to be given even if the right answer was not known. The next trial started immediately after the response on T2. Participants were also instructed to keep central fixation throughout the whole trial, until the onset of the response screen. We did not record eye movements by an eye tracking device, because none was available in our Krakow lab. We had shown in previous studies that the LVF advantage in T2 identification cannot be explained by an eye movement bias, as the effect was still obtained even under strict control of fixation by means of infrared oculography (Verleger et al., 2009; Experiment 3; Verleger et al., 2013).

Varying the lag between T1 and T2 (1, 3, or 5), the side of T1 (left, right), and the side of T2 (left, right) resulted in 12 combinations of T1-T2 sequences, which were replicated 36 times (432 trials) in random order for either task condition (single and dual target). These two conditions were presented in two separate blocks, with order counterbalanced between participants. The whole experiment lasted up to one and a half hour. Both conditions were preceded by two short practice blocks, each consisting of six trials. During the first practice block, stimuli were presented in slow motion, with a display time of 500 ms, instead of 117 ms. The second practice block was performed with normal settings. During these practice trials, feedback about accuracy was given after each response.

Two-stream RSVP task with fewer distractors. The task is illustrated in **Figure 1**. As a major change from the standard task, distractor letters occurred only directly before and after T1 and T2 (with one obvious exception at lag 1, where T2 followed T1 directly, as in the standard procedure). All other distractor letters were removed, and the fixation-cross was presented alone on the screen instead. All other aspects were identical to the standard task. In particular, the intervals between fixation point onset and T1 remained the same as in the standard procedure: 800 ms fixation period plus an interval equivalent to the five, seven, or nine letter pairs preceding T1. By this, participants did not precisely know when T1 would occur. Also, the interval between T2 offset and the end of the trial remained the same as in the standard task.

Data analysis

In the dual-target task, the percentage of correctly identified T1 was calculated from all trials, and the percentage of correctly identified T2 was computed from all correctly identified T1 trials. In the single-target task the percentage of correctly identified T2 was calculated from all trials. Accuracies of T1 and T2 identification in the dual-target task were analyzed separately by means of a 2 × 2 × 3 × 2 repeated measures analysis of variance (ANOVA)

with Target Side (left, right; with target being T1 or T2, depending on analysis), Side Change (same side or different side of T1 and T2), and Lag (1, 3, or 5) as within-subject factors and the between-subjects factor Number of Distractors (standard number of distractors vs. reduced number of distractors). Since our interest was in VF asymmetry, effects of Side Change, Lag and Number of Distractors will be reported only if interacting with Target Side. To compare T2 identification between dual and single target tasks, a 5-way ANOVA was conducted with the additional within-group factor Task (single vs. dual-target task), focusing on moderating effects of Task on the LVF, i.e., on interactions of Task × Target Side.

RESULTS

Mean identification rates of T1 and T2 are compiled in **Table 1** and presented in **Figure 2**.

T1 identification in the dual-target task

T1 was correctly identified in 90% of trials (**Figure 2**, upper left panel), somewhat better with the standard number of distractors than with few ones, though not significantly so ($F_{(1, 40)} = 2.8$, $p = 0.10$, $\eta^2 = 0.06$), and equally well in LVF and RVF (T1 Side: $F < 1.0$), except for a RVF advantage at lag 1 (T1 Side × Lag: $F_{(2, 80)} = 6.7$, $p = 0.003$, $\eta^2 = 0.14$; T1 Side at Lag 1: $F_{(1, 40)} = 5.3$, $p = 0.026$).

T2 identification in the dual-target task

T2 was correctly identified in 82% of T1-correct trials (**Figure 2**, lower left panel). As expected, a clear-cut LVF advantage was observed ($F_{(1, 40)} = 72.0$, $p < 0.0001$, $\eta^2 = 0.64$), modulated by Side Change and Lag, as indicated by the T2 Side × Side Change × Lag interaction ($F_{(2, 80)} = 11.6$, $p < 0.0001$, $\eta^2 = 0.22$). When T1 and T2 were on the same side, the LVF advantage was very small at lag 1 and increased at lags 3 and 5 (T2 Side × Lag for same side T2: $F_{(2, 80)} = 10.4$, $p < 0.0001$). When T1 and T2 were on opposite sides, the LVF advantage slightly decreased from lag 1 to lag 5 (T2 Side × Lag for the opposite-side T2: $F_{(2, 80)} = 3.7$, $p = 0.035$). The LVF advantage was significant at each of the six Side Change the small 2% LVF advantage when T2 occurred at lag 1 on the same side as T1 (all $Fs_{(1, 40)} \geq 6.1$, $p \leq 0.018$).

Crucially, the T2 Side effect was the same for either Number of Distractors condition (main effect of Number of Distractors and interaction with T2 Side: $F < 1.0$), indicating no difference in the LVF advantage between the two conditions. Other interactions with these two factors were also not significant, except the marginally significant T2 Side × Lag × Number of Distractors interaction ($F_{(2, 80)} = 2.7$, $p = 0.076$, $\eta^2 = 0.06$), which reflects the slightly decreased LVF advantage at Lag 5 when the number of distractors was reduced (T2 Side × Number of Distractors for Lag 5 only: $F_{(1, 40)} = 4.0$, $p = 0.051$; LVF vs. RVF at lag 5 for reduced number of distractors: $F_{(1, 19)} = 24.6$, $p < 0.001$), possibly due to a ceiling effect with left-side targets (**Figure 2**).

T2 identification in single-target vs. dual-target task

When T1 was ignored, T2 was correctly identified in 92% of all trials (lower right panel of **Figure 2**), 10% better than in the dual-target task ($F_{(1, 40)} = 28.6$, $p < 0.0001$, $\eta^2 = 0.41$). These

Table 1 | Percentages of correct target identification (with standard deviations) under each condition of Experiment 1.

Lag	1				3				5			
Side of the other target	Same		Opposite		Same		Opposite		Same		Opposite	
Target VF	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
T1												
Standard procedure	89.3 (10.5)	92.6 (6.6)	90.3 (9.7)	91.4 (6.9)	91.2 (9.5)	90.0 (6.7)	92.8 (6.9)	91.3 (7.3)	92.9 (8.1)	91.3 (7.0)	92.2 (7.0)	92.4 (7.3)
Reduced number of distractors	87.4 (7.9)	90.3 (10.2)	86.4(10.2)	88.7 (9.8)	85.6 (10.7)	89.4 (9.4)	87.1 (10.5)	86.8 (12.2)	88.5 (7.8)	87.9 (8.7)	86.8 (9.8)	85.8 (13.0)
T2/T1 DUAL TARGET TASK												
Standard procedure	97.6 (3.0)	96.1 (3.7)	70.0 (19.6)	53.0 (18.6)	85.2 (11.2)	76.5 (15.1)	86.4 (13.1)	72.6 (19.3)	92.2 (7.8)	78.0 (13.2)	91.2 (10.7)	79.6 (16.6)
Reduced number of distractors	96.4 (5.6)	93.8 (5.2)	67.5 (17.6)	49.9 (14.6)	87.0 (10.7)	77.9 (14.3)	87.8 (9.8)	71.5 (18.1)	93.1 (7.5)	87.2 (9.8)	95.3 (7.2)	85.5 (11.4)
T2 SINGLE TARGET TASK												
Standard procedure	99.0 (1.6)	96.5 (3.9)	96.3 (5.5)	83.3 (11.6)	95.1 (5.7)	89.3 (6.7)	94.4 (4.7)	85.2 (12.1)	95.1 (5.7)	86.4 (8.6)	94.7 (5.5)	87.8 (13.9)
Reduced number of distractors	95.1 (11.7)	93.2 (13.7)	94.6 (19.1)	89.2 (18.3)	93.1 (17.7)	90.1 (18.5)	93.5 (18.3)	90.0 (17.5)	93.8 (19.0)	91.9 (17.6)	95.4 (16.7)	92.2 (18.3)

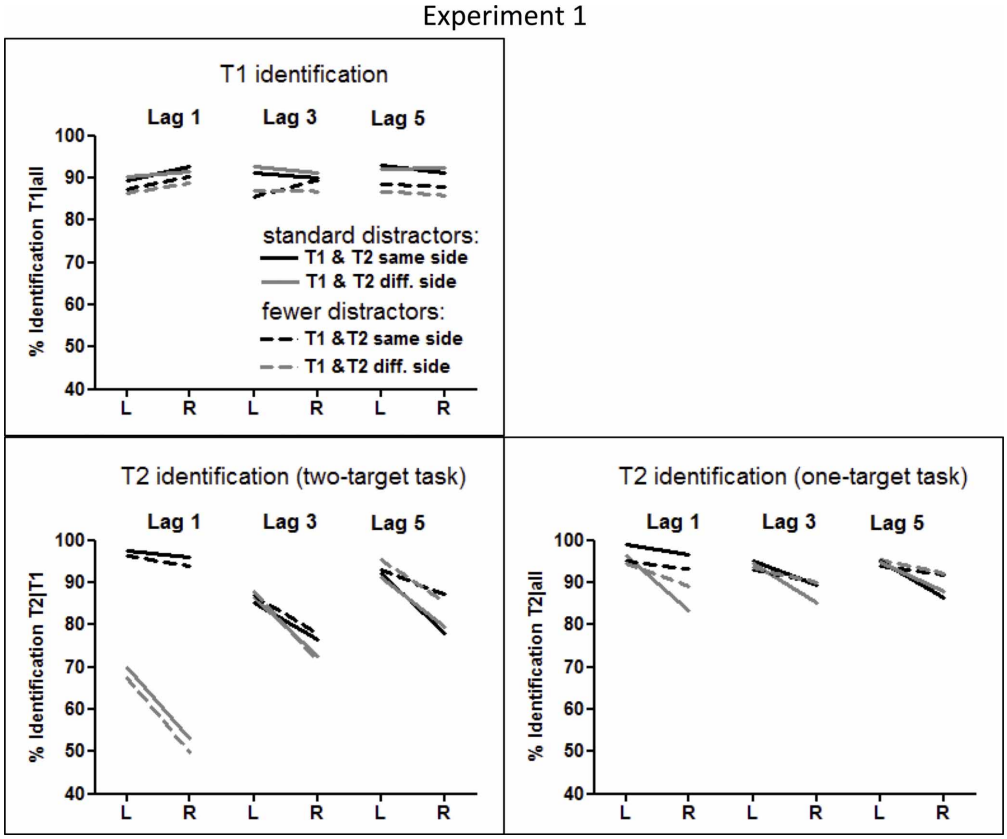


FIGURE 2 | Identification rates of T1 and T2 in Experiment 1. Results are displayed for T1 in the **upper left panel**, for T2 from the dual-target task in the **lower left panel**, and for T2 from the single-target task in the **lower right panel**.

benefits from having to identify one target only were larger for RVF than for LVF (Task × T2 Side: $F_{(1,\ 40)} = 16.8$, $p < 0.0001$, $\eta^2 = 0.29$). Yet there was still a LVF advantage in separate analysis of the single-target task ($F_{(1,\ 40)} = 35.0$, $p < 0.0001$, $\eta^2 = 0.46$), although decreased in comparison to the dual-target task. This decrease of the LVF advantage equaled only 1% when T1 and T2 occurred on the same side, whereas when T1 and T2 were on different sides, the LVF advantage decreased about 8% (Task × T2 Side × Side Change: $F_{(1,\ 40)} = 5.0$, $p = 0.031$, $\eta^2 = 0.11$; Task × T2 Side for same-side T2: $F_{(1,\ 40)} = 8.4$, $p = 0.006$, $\eta^2 = 0.17$; Task × T2 Side for different-side T2: $F_{(1,\ 40)} = 13.0$, $p = 0.001$, $\eta^2 = 0.25$). This interaction was only marginally modified by Lag (Task × T2 Side × Side Change × Lag: $F_{(2,\ 80)} = 2.3$, $p = 0.10$, $\eta^2 = 0.05$), but when analyzed for each lag separately, the Task × Side Change modulation of the LVF advantage was in fact true only at lag 1 (Task × T2 Side × Side Change at lag 1: $F_{(1,\ 40)} = 7.0$, $p = 0.011$, at lag 3: $F_{(1,\ 40)} = 2.1$, $p = 0.15$, and at lag 5: $F_{(1,\ 40)} < 1.0$, $p =$ n.s.). Thus, these complex interactions simply reflected that the small LVF advantage in the dual-target task for same-side lag-1 T1-T2 sequences, where identification rates were at ceiling, could hardly be further reduced, whereas the large LVF advantage in the other combinations of T1-T2 sequence shrank in the single-target task. This reduction of the large LVF advantage for different-side T2 in the single-target task, where the immediately preceding T1 could be ignored, was most probably related to the fact that the general difference between same-side and different-side T2 at lag 1 was reduced (but not completely abolished) from the dual-target to the single-target task. Thus, the Task × Side Change × Lag interaction amounted to $F_{(2,\ 80)} = 154.2$, $p < 0.0001$, $\eta^2 = 0.79$, and the Task × Side Change interaction for lag 1 only, amounted to $F_{(1,\ 40)} = 254.5$, $p < 0.0001$.

Of importance, although the right panel of **Figure 2** may suggest that the LVF advantage was smaller in the single-target task with fewer distractors than with the standard number of distractors, particularly with lags 1 and 3 when T1 and T2 were on different sides, no interaction of Task × Number of Distractors × T2 Side became significant (F's ≤ 2.0, $p \geq 0.16$).

DISCUSSION

The results of the two-stream RSVP with the standard series of distractors showed, as expected, a clear-cut LVF advantage in T2 identification, while T1 was identified equally well in both VFs, with a small trend to a RVF advantage. Thereby, previous results of studies using this task were replicated (e.g., Verleger et al., 2009; Śmigasiewicz et al., 2010; including studies where eye movements were strictly controlled by means of

an eye tracker: Verleger et al., 2009; Experiment 3; Verleger et al., 2013)[1], constituting an appropriate reference for the task with fewer distractors.

The reduction of distractors was supposed to decrease verbal load, thereby testing the assumption that the LVF is a consequence of overloading the left hemisphere with verbal input. As the experiment has shown, this manipulation had no impact on the LVF advantage, except for the marginally decreased asymmetry at lag 5 where performance generally improved with reduced number of distractors (see **Figure 2**). The crucial point might have been that with lag 5, in contrast to lag 1 and lag 3, stimulus streams differed between the conditions with full and with reduced number of distractors. With lag 1 and lag 3 between T1 and T2, the lags were filled by distractors equally in the full-number and the reduced-number-of-distractors conditions. But for lag 5, there was an empty interval at frames 2 and 3 after T1 in the reduced-distractors condition, followed by the onset of distractors preceding T2 at frame 4. Therefore, as soon as this empty interval occurred (at frame 2), participants could know that T2 would follow three frames (=350 ms) later, reducing temporal uncertainty. Moreover, the reappearance of distractors at frame 4 might have produced an alerting effect. The latter effect might be less relevant because a similar alerting effect is supposed to occur by the sudden onset of distractors before T1 in the reduced-distractors condition, yet T1 identification did not improve. So it was probably by the reduction of temporal uncertainty (cf. Niemi and Näätänen, 1981) that performance generally improved at lag 5 when the number of distractors was reduced. The corresponding reduction of LVF advantage in this condition may be a ceiling effect due to the higher overall accuracy at lag 5 in the task with fewer distractors, cf. Boles et al. (2008) for an extensive discussion of the dependence of measures of asymmetry on the overall performance level. It appears that with fewer distractors, the task of T2 identification at lag 5 became very similar to the task of T1 identification (thus comparably easy) due to the gap without stimulation occurring between T1 and T2 with lag 5. This seems to be confirmed by the fact that T2 at lag 5 was identified distinctly worse than T1 with the standard number of distractors ($p = 0.001$), while there was no significant difference with the reduced number of distractors ($p = 0.11$), in contrast to lag 3 and lag 1 where the difference between T1 and T2 identification was significant in both conditions. We might therefore conclude that the results of Experiment 1 suggest no relationship between verbal load produced by background letter stimuli and the LVF advantage in T2 identification under the dual-target condition, which opts against the overload hypothesis.

It may be argued, though that the reduced number of distractors still was sufficiently high to produce overload. To detail, there were still eight letters preceding T2, consisting of the pair of distractors preceding T1, of T1 and its accompanying distractor, of the pair following T1, and of the pair preceding T2. These eight letters (4 pairs × 2 sides), according to the LH overload hypothesis, would have to be processed by the LH and might have overloaded it to an extent not less than, say, when twenty letters had preceded. However, this argument does not apply at the same extent to the lag-1 condition. To detail, in this case, four letters only preceded T2 in the reduced-distractors condition, consisting of the pair of distractors preceding T1 and of T1 and its accompanying distractor. Yet also this appreciable reduction of the number of distractors did not have any moderating effect on the LVF advantage. It may still be argued that already these four preceding letters had completely overloaded the LH. However, testing this assumption by further reducing the number of distractors becomes difficult within the present paradigm because distractors preceding and trailing T1 would then have to be abolished altogether, which entails changes in overall discriminability of T1 and T2 and in general difficulty of the task. Therefore, what may be concluded is that the overload hypothesis was not confirmed as far as could be tested within the limits of the present task.

The present experiment also showed that when T1 had to be ignored, the LVF advantage decreased, as compared to the dual-target task. This reduction of VF asymmetry might be interpreted as supporting the overload hypothesis, because ignoring T1 decreases the verbal demands of the task when the LH verbal system is released from the necessity of T1 processing. On the other hand, this reduction of VF asymmetry might simply be due to a ceiling effect in the LVF. Being already high in the dual-target task, T2 identification in the LVF had much less space to improve in the single-target task compared to T2 presented in the RVF. In favor of this interpretation as a ceiling effect, the reduction of VF asymmetry closely followed improvement of T2 accuracy in the single-target task in general, being largest when T2 occurred at lag 1 in the stream different from T1. Importantly, the fact that there was still some LVF advantage present in the single-target task indicates that explicit identification of T1 is not necessary to evoke VF asymmetry in identification of the following T2 [cf. results by Nieuwenstein et al. (2009), for effects of ignoring T1 in the task with one central stream], which also suggests that this VF asymmetry is not related to the overload of the LH by target letters.

To summarize, the LVF advantage for T2 was neither abolished by reducing the number of distractors nor by letting T1 be ignored. These two results may be interpreted as converging evidence against the LH overload hypothesis. On the other hand, there were still some letters preceding T2 and possibly producing LH overload even when the number of distractors was most reduced, and the possibility of ignoring T1 did reduce (though not abolish) the LVF advantage. Therefore, these results cannot be taken as definite answer to the studied question either.

EXPERIMENT 2A

Here, we introduced another strategy to further investigate the overload hypothesis. Instead of decreasing the load of the LH, we attempted to overload the RH. To this end, we used stimuli supposed to be preferentially processed by the RH. Lateralization in processing of human faces by the RH seems to be comparable to lateralization in processing verbal information by the LH

[1]This shows that the asymmetry cannot be explained by uncontrolled eye movements. Another argument (pointed out by one reviewer of this paper) is that if the LVF advantage were eye movements artifacts, the asymmetry should be consistent for both T1 and T2, which was not the case in any of the two stream RSVP studies conducted thus far.

(see Dien, 2009, for meta-analysis). Hence, according to the overload hypothesis, using images of faces as targets and distractors would result in an asymmetry reversed from using letters and digits, leading to a RVF advantage (see for similar ideas Hellige et al., 1979; Holländer et al., 2005). On the other hand, if the asymmetry occurs due to some general RH advantage, the LVF advantage will still be observed, independently of the type of stimuli.

METHOD

Participants

Participants were recruited from the same population and fulfilled the same inclusion criteria as in Experiment 1. From the originally twenty-two participants, one person was excluded due to accuracy of T1 identification near chance level (17%). The remaining participants were 17 females and 4 males, their mean age was 19.5 ($SD = 0.9$), and their mean score in the Edinburgh Handedness Inventory was 84.0 ($SD = 19.1$).

Stimuli, apparatus, and procedure

Pictures of faces were presented instead of letters and digits. Twenty-six pictures of male faces and six pictures of female faces were taken from the NimStim Set of Facial Expression (Tottenham et al., 2009; http://www.macbrain.org/resources.htm). All pictures showed emotionally neutral face expression. These stimuli were 10 mm wide and 15 mm high (0.7° × 1.0° visual angle), somewhat larger than the letters used in Experiment 1. Distance between the inner edge of pictures and the fixation point was 11 mm (0.8°). The first target (T1) was one of six pre-selected male faces displayed on a red background, in analogy to the red T1 letter in Experiment 1. The second target (T2) was one of the six female faces displayed on a white background, in analogy to the digit T2 in Experiment 1. The distractor set consisted of the remaining twenty male faces displayed on white background. All other parameters of the task and procedure remained the same as in Experiment 1. An example of the stimuli is depicted in **Figure 3**.

The single-target condition was omitted in Experiment 2 [similarly as in the previous two-stream RSVP studies by Śmigasiewicz et al. (2010) and Verleger et al. (2009, 2010, 2011)], because to test the RH overload hypothesis we only needed to investigate whether the normally observed LVF advantage in T2 identification under the dual-target condition will reverse to a RVF advantage.

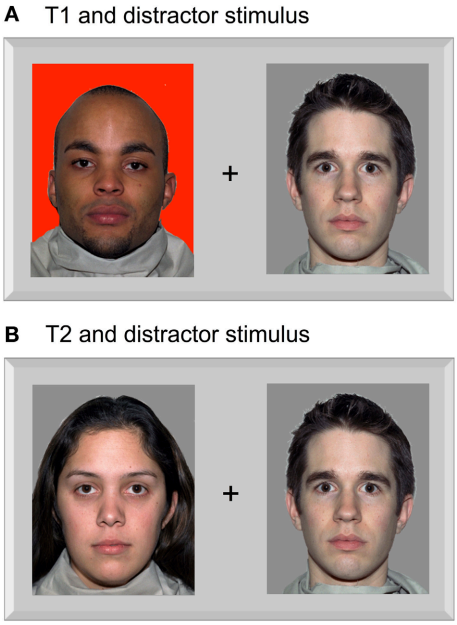


FIGURE 3 | An example of the face-stimuli used in Experiment 2 as T1 (A) and T2 (B). Pictures were taken from the NimStim Set of Facial Expression (Tottenham et al., 2009; http://www.macbrain.org/resources.htm).

RESULTS

Mean identification rates of T1 and T2 are presented in **Table 2** and on the left side of **Figure 4**.

T1 identification

T1 was correctly identified in 64% of trials (thus significantly worse than letter-T1 in Experiment 1, $F_{(1,\ 41)} = 153.5$, $p < 0.0001$, for the comparison to the procedure with standard stimuli), and 9% better in the LVF than in the RVF ($F_{(1,\ 20)} = 9.4$, $p = 0.006$, $\eta^2 = 0.32$). When T1 occurred on the same side as the following T2, this LVF advantage was not significant at lag 5 ($F_{(1,\ 20)} = 1.8$, $p = 0.18$, $\eta^2 = 0.09$; interaction T1 side × Lag for T1 occurring at the same side as T2: $F_{(2,\ 40)} = 3.8$, $p = 0.041$, $\eta^2 = 0.16$; three-way interaction T1 Side × Side Change × Lag: $F_{(2,\ 40)} = 5.6$, $p = 0.011$, $\eta^2 = 0.22$). In the opposite-side condition, the LVF advantage equaled 9% and did not differ between lags ($F_{(2,\ 40)} = 1.3$, $p = 0.27$, $\eta^2 = 0.06$).

T2 identification

The T2-face was identified in only 28% of T1-correct trials (less than the digit-T2 in Experiment 1, $F_{(1,\ 41)} = 229.5$, $p < 0.0001$). Crucially, T2 was still identified significantly better in the LVF than in the RVF (6% difference, $F_{(1,\ 20)} = 19.7$, $p < 0.0001$, $\eta^2 = 0.49$). The LVF advantage marginally increased at lag 5 (T2 Side × Lag: $F_{(2,\ 40)} = 3.0$, $p = 0.066$, $\eta^2 = 0.13$). None of the other interactions with T2 Side was significant.

DISCUSSION

A clear LVF advantage was observed in identification of face-T2, in stark contrast to the RVF advantage predicted by the overload hypothesis. Already face-T1 was identified much better in the LVF. This is consistent with RH dominance in face processing (Dien, 2009). On the other hand, the fact that the LVF advantage already occurred with T1 might reflect the increased difficulty of this task, such that the RH dominance in attentional selection becomes apparent already with T1. This increased task difficulty by using faces instead of letters and digits severely compromised overall task performance, reducing accuracy in identification of both T1 and T2, as compared to the standard procedure with alphanumerical stimuli. Faces might be too similar to each other, thereby being much harder to distinguish than letters or numbers. Such similarity of stimuli would provide much greater burden

Table 2 | Percentages of correct target identification (with standard deviations) in Experiments 2A, 2B, (with faces) and 3 (with shapes).

Lag	1				3				5			
Side of the other target	Same		Opposite		Same		Opposite		Same		Opposite	
Target VF	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
T1												
Experiment 2A	68.1 (12.2)	56.9 (10.5)	67.6 (13.4)	60.2 (14.0)	69.3 (13.1)	58.1 (13.0)	68.9 (13.6)	60.8 (12.5)	66.8 (13.8)	62.0 (12.2)	70.8 (13.3)	59.4 (13.6)
Experiment 2B	72.7 (11.4)	59.2 (10.8)	76.0 (14.0)	67.2 (10.1)	76.9 (14.4)	67.0 (14.3)	76.0 (12.7)	65.3 (12.8)	78.3 (10.8)	64.6 (12.2)	79.7 (10.7)	67.2 (12.4)
Experiment 3	82.4 (11.1)	87.7 (9.9)	82.3 (12.2)	86.0 (8.5)	79.8 (13.5)	83.2 (11.7)	82.2 (10.7)	85.5 (9.5)	79.7 (13.5)	87.0 (9.2)	80.1 (11.4)	86.8 (9.0)
T2/T1 DUAL TARGET TASK												
Experiment 2A	25.1 (13.7)	21.7 (12.9)	21.9 (10.5)	18.6 (7.8)	29.4 (14.5)	28.2 (14.7)	27.6 (11.8)	22.7 (12.8)	39.5 (22.0)	29.2 (17.9)	39.5 (16.9)	28.2 (9.9)
Experiment 2B	78.1 (16.8)	74.7 (16.2)	67.2 (11.1)	60.2 (13.6)	77.7 (12.5)	71.1 (16.7)	76.9 (14.1)	72.1 (13.4)	79.0 (14.0)	77.0 (15.1)	78.3 (15.4)	74.6 (14.3)
Experiment 3	55.3 (30.3)	51.5 (27.0)	33.3 (16.3)	20.2 (13.0)	48.0 (22.4)	39.6 (21.4)	36.7 (23.0)	28.9 (19.2)	52.6 (25.4)	37.4 (23.1)	48.5 (27.3)	37.4 (22.5)

for working memory than in case of letters or digits, and may also somehow confuse participants, which together increased the number of errors.

EXPERIMENT 2B

Because the procedure applied in the previous experiment proved to be very difficult, we conducted an additional experiment, attempting to increase overall accuracy by reducing the sets of T1 and T2 from six to only two stimuli. Although this change from six to two targets may entail increasing the number of lucky guesses, from 17 to 50%, it allows for avoiding confusions due to high similarity between targets and the resulting overly high demands on memory. The expected higher accuracy should provide more reliable evidence in favor or against the overload hypothesis.

METHOD

Participants

Participants were recruited from the same population and fulfilled the same inclusion criteria as in Experiment 1. The sixteen participants were 1 man and 15 women, their mean age was 20.0 ($SD = 1.4$), and their scores in the Edinburgh Handedness Inventory were 83.7 ($SD = 17.3$).

Stimuli, apparatus, and procedure

The sizes of the T1 and T2 sets were reduced from six to two. The number of distractor faces remained the same. The responses were matched to the requirement to select one of two alternatives only. Participants responded by pressing the "F" or "J" keys for T1 identification and the "1" or "4" keys for T2 identification, indicated by the response screens that followed the RSVP series in each trial like in the preceding experiments. All other parameters of stimuli, apparatus, and procedure remained the same as in Experiment 2A.

RESULTS

Mean identification rates of T1 and T2 are presented in **Table 2** and on the right side of **Figure 4**.

T1 identification

T1 was correctly identified in 71% of trials. Similar to Experiment 2A, we observed a clear LVF advantage, which equaled 11% ($F_{(1,\ 15)} = 12.3$, $p = 0.003$, $\eta^2 = 0.45$) and did not interact with other factors.

T2 identification

The overall identification rate amounted to 74%. Crucially, left T2 was identified 5% better than right T2 ($F_{(1,\ 15)} = 10.2$, $p = 0.006$, $\eta^2 = 0.40$). No interaction of this effect with other factors was significant.

DISCUSSION

Replacing alphanumeric stimuli by faces, and in particular the red-letter T1 by a face on red background and the digit-T2 by a female-face T2, again resulted in LVF advantage in both T1 and T2 identification. Although the asymmetry was smaller than the effect obtained with the standard alphanumeric stimuli in Experiment 1, the direction of the effect provides clear evidence

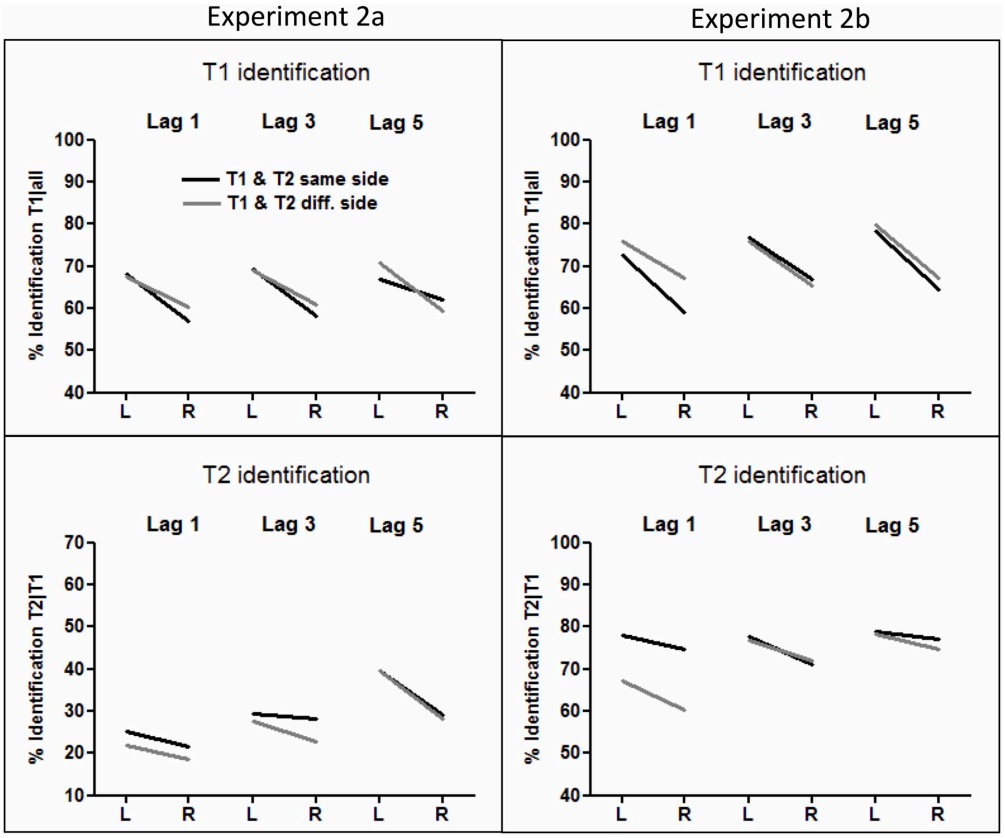


FIGURE 4 | Rates of T1 and T2 identification in Experiments 2A (left panel) and 2B (right panel). T1 identification rates were calculated from all trials, and T2 identification rates were computed from all correctly identified T1 trials.

against the overload hypothesis, which predicted a LVF/RH disadvantage. The smaller effect size of the LVF advantage, as compared to the standard procedure, might be related to the different type of stimuli or to the larger difficulty of target discrimination, which resulted in lower accuracy.

EXPERIMENT 3

In order not to prematurely reject the overload hypothesis on the basis of one particular type of stimuli only, the third experiment was conducted with another type of stimuli that is supposed to be processed preferentially by the RH. In particular, processes of coding and distinguishing between global and configural properties of objects or shapes have been shown to be right-lateralized (Gazzaniga, 2000; Floel et al., 2004; Hellige et al., 2010). Hence, in order to engage the RH more than the LH and to decrease the engagement of the left verbal system to a minimum, irregular geometric shapes were here used as T1 and as distractor stimuli. The shapes were all new, designed for the purpose of the study, thus were unknown to participants, and unnamable or at least very difficult to name, especially when displayed rapidly in serial presentation. Choosing this kind of non-verbal stimuli should prevent participants from providing verbal or analytic coding (cf. Hellige et al., 1979). As T2, a hexagon with a gap on one of its sides was used, in order to create a category of stimuli that would be relatively similar to the other shapes, but at the same time noticeably distinguishable, like digits among letters. According to the overload hypothesis, the pattern of VF asymmetry will be reversed from the standard procedure, i.e., a RVF advantage is expected. Alternatively, if the LVF advantage occurs due to RH dominance, the general pattern of asymmetry would remain principally unchanged.

METHOD

Participants

Twenty-one participants took part in the experiment. Two of them had to be excluded due to high error rates in identifying T1 (32% correct, the average from the other 19 participants being 83%). In the remaining sample 15 were female. The average age was 20.0 ($SD = 1.4$), with average Edinburgh Handedness Inventory scores of 81.7 ($SD = 22.0$).

Stimuli, apparatus, and procedure

The RSVP task used in this experiment was a faithful copy of the task from Experiment 2A, but irregular shapes were presented instead of faces. The stimuli are illustrated in **Figure 5**. Shapes were designed especially for the purpose of the study. All of them were irregular, unknown, and rather difficult to name

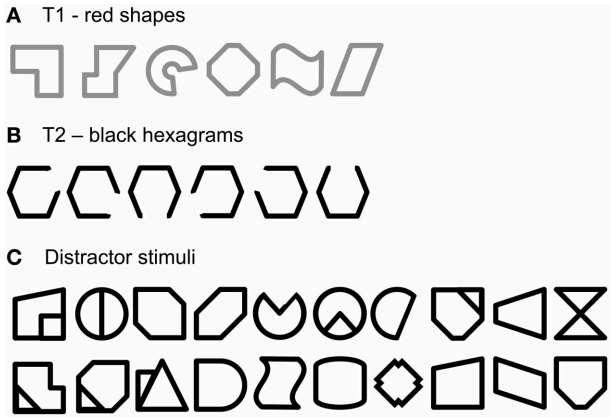


FIGURE 5 | Stimuli used in Experiment 3 as T1 (A), T2 (B), and distractors (C). Red color is replaced here by gray.

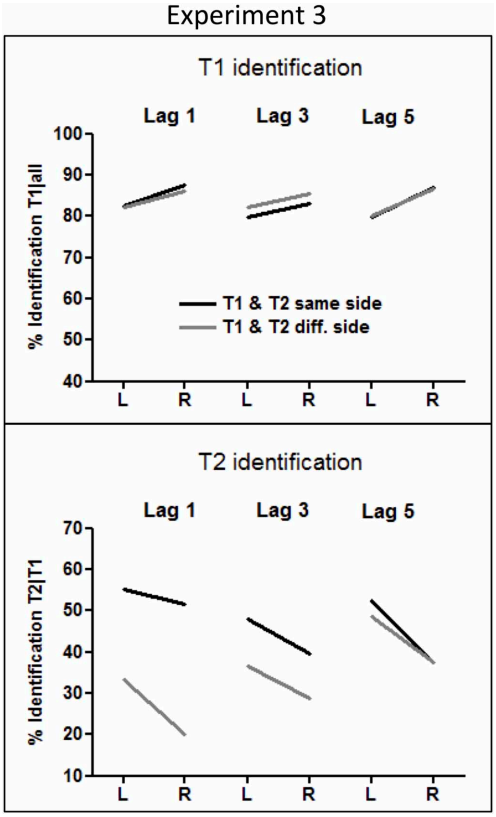


FIGURE 6 | Rates of T1 and T2 identification in Experiment 3. T1 identification rates were calculated from all trials, and T2 identification rates were computed from all correctly identified T1 trials.

or verbalize. The distractor set consisted of 20 black shapes. The set of T1 consisted of six red shapes, similar to, but different in details from distractors. The set of T2 included six hexagons with a gap: each hexagon had one of its six sides removed. As before, participants were asked to identify T1 and T2. At the end of each trial the response screen displayed the six targets and the participants were to press the corresponding key on the computer keyboard. As in Experiments 1 and 2A, the mapping of T1 and T2 to keys was 'D', 'F', 'G', 'J', 'K', and 'L' for T1s, and from '1' to '6' for T2s.

RESULTS

Mean identification rates of T1 and T2 are presented in **Table 2** and in **Figure 6**.

T1 identification

Participants correctly identified shape-T1 in 83% of trials. Surprisingly, shape-T1s were identified about 5% better in the RVF than in the LVF ($F_{(1,\ 18)} = 18.4$, $p < 0.0001$, $\eta^2 = 0.50$). Other effects of T1 Side were not significant.

T2 identification

The overall accuracy in hexagram-T2 identification was 41%. A clear LVF advantage, amounting to 10%, was obtained ($F_{(1,\ 18)} = 22.6$, $p < 0.0001$, $\eta^2 = 0.55$). As indicated by the interaction of T2 Side × Side Change × Lag, $F_{(2,\ 36)} = 4.3$, $p = .024$, $\eta^2 = 0.19$, this LVF advantage increased across lags when T1 and T2 occurred on the same side (T2 Side × Lag: $F_{(2,\ 36)} = 6.1$, $p = 0.007$), from the marginally significant 4% effect at lag 1 ($F_{(1,\ 18)} = 3.3$, $p = 0.087$), to 8% at lag 3 ($F_{(1,\ 18)} = 7.0$, $p = 0.016$), and to 15% at lag 5 ($F_{(1,\ 18)} = 15.8$, $p = 0.001$), and a stable LVF advantage of 11% across lags was observed when T1 and T2 occurred on different sides (T2 Side × Lag: $F < 1.0$).

DISCUSSION

The overall pattern of T2 identification rates across all conditions was very similar to the results obtained in the standard two-stream RSVP task with letters and digits. In particular, a clear LVF advantage in T2 identification was observed despite replacing all alphanumeric stimuli by shapes, and the digit-T2 by a hexagon-T2. Therefore, the results seem to disprove once again the overload hypothesis and suggest that the LVF advantage in T2 identification is independent of the type of stimuli used.

However, the red-shape T1 was identified better in the RVF than in the LVF. One possible explanation of this effect is that the requirement to keep the particular six types of red-shape T1 in mind overloaded visual working memory of the RH to such an extent that a reversed VF asymmetry was already produced in T1 identification, analogously to paradoxical effects of LVF advantage observed in a visuo-spatial verbal task when the LH was overloaded by a concurrent verbal memory task (Hellige et al., 1979). This account would, therefore, concede that overload is a potent factor in these RSVP tasks. However, since the overload account of the LVF advantage of T2 identification requires the LH to be overloaded, rather than the RH, this overload of the RH, although presumably present, cannot account for the obtained result.

A nearby alternative account of the better identification of T1 in the RVF is that this identification might require some specific processing capability in which the LH is more efficient, just as letters are supposed to do (cf. the slight RVF advantage for T1 in

Experiment 1). For example, distinguishing between the specific T1 exemplars might require processing of spatial details rather than processing the global form. Processing of spatial details might be better accomplished by the LH (e.g., Robertson and Lamb, 1991) or some subset of the T1 shapes might have been verbally coded by participants. In this case, in terms of the overload hypothesis, it would be the LH that was overloaded by its successful identification of T1, reducing its ability to identify T2. Thus, if this alternative is true the current experiment did not disprove the overload hypothesis.

GENERAL DISCUSSION

When two consecutive targets, T1 and T2, are presented in two simultaneous RSVP streams, T2 is identified much better in the LVF than in the RVF (Holländer et al., 2005; Verleger et al., 2009). According to the overload hypothesis (Hellige et al., 1979; Verleger et al., 2010), this asymmetry might reflect a LH disadvantage due to an overload of the LH's verbal processing system by the two-stream rapid serial presentation of distractor and target letters. If this hypothesis holds true, the LVF advantage should largely decrease or even be completely eliminated when the number of letter-distractors is drastically reduced or when the letter-T1 does not have to be identified. Analogously, replacing letters and digits by stimuli which the RH is supposed to be specialized for (e.g., faces or irregular shapes) should overload the RH, thereby decrease its processing efficiency and lead to LVF disadvantage in T2 identification.

The results of the present study provide evidence on this issue. Most convincing evidence against the overload hypothesis was provided by Experiment 2, where a LVF advantage was obtained for face T2 stimuli embedded among face distractors and following face T1 stimuli, in the same direction as was obtained in Experiment 1, and in previous studies, for digit T2 embedded among letters and following letter T1 stimuli. Importantly, this LVF advantage for face-T2 in Experiment 2 occurred in spite of a distinct LVF advantage already for face-T1. This face-T1 asymmetry, suggesting an advantage of the RH in identifying these faces, was even more marked than the reversed asymmetry (with a slight RVF advantage) obtained with the letter-T1 in Experiment 1. Thus, the overload hypothesis predicts that T2 asymmetry should be reversed, from a LVF advantage with alphanumeric stimuli to a RVF advantage with faces. This prediction was not borne out. Converging, though not unambiguous, evidence was provided by the other two experiments. First, the LVF advantage in T2 identification remained, despite decreased verbal load by reducing the number of background letter distractors (Experiment 1). Second, replacing letters and digits by irregular shapes and hexagrams (Experiment 3) did not reverse the asymmetry. The LVF advantage was still present with those stimuli, contrary to the predictions of the overload hypothesis. Thus, the study provides evidence that this asymmetry is largely independent from the verbal load level (Experiment 1), from the type of stimuli used as both targets and distractors (Experiments 2 and 3), as well as from the presence and direction of VF asymmetry in T1 identification (Experiment 3).

In support of the overload hypothesis, it may be argued for Experiment 1 (cf. 2.3, above) that the reduction of number of distractors in Experiment 1 was not sufficiently drastic, with even four preceding stimuli (in case of lag 1) perhaps being enough to overload the LH. Moreover, waiving the requirement to identify T1 (Experiment 1) reduced the LVF, which conforms to the overload hypothesis. Correspondingly, for Experiment 3 (cf. 5.3, above) the RVF advantage for identifying the shape-T1 puts into doubt whether these shapes were as specifically processed in the RH as we would have expected them to be (and as the faces in Experiment 2 probably were). Thus, evidence is still not conclusive, in spite of the wide variation in stimuli used in our experiments.

Yet, the most parsimonious explanation of the constantly occurring LVF advantage in T2 identification is that the effect is brought about by lateralization of some domain-general processing system, plausibly an attentional or perceptual mechanism, as has been hypothesized in previous studies (Holländer et al., 2005; Verleger et al., 2009, 2011; Śmigasiewicz et al., 2010). Evidence that conforms to both the attentional and the perceptual explanations of the LVF advantage was obtained in recent two-stream RSVP studies by recording two components of event-related electroencephalogram potentials (ERPs) which were the N2pc evoked by T1 and T2, and the visual evoked potentials (VEPs) triggered by the stream of distractors. N2pc is defined as a negative deflection recorded above the visual cortex contralateral to attended stimuli, as compared with responses to irrelevant non-target or unattended stimuli, and is interpreted as an indicator of attentional selection (Luck et al., 1993; Eimer, 1996; Wascher and Wauschkuhn, 1996). Shorter latencies of the T2-evoked N2pc were obtained in the RH than in the LH, suggesting RH superiority in speed of T2 selection (Verleger et al., 2009, 2011). Furthermore, the visual potentials evoked by the distractor streams preceding T1 were reliably leading at the RH by a few milliseconds compared to the LH (Verleger et al., 2011, 2013), which suggests generally faster perceptual processing of visual events in the RH than in the LH in this task (cf. Okon-Singer et al., 2011). This general speed advantage of the RH might contribute to the efficiency of the RH in singling out the rapidly presented target-stimuli within the two streams of distractors.

The attentional explanation appears to be in line with the neuroanatomical model of attentional selection proposed by Corbetta and Shulman (2002). Those authors have provided many pieces of evidence for distinguishing between two neural systems dedicated for attentional selection: the dorsal frontoparietal network controlling endogenous orienting of attention, which is driven by expectations or predictive cues, and the ventral frontoparietal network controlling selection of targets or other potentially relevant stimuli that occur outside of the current focus of attention (see Corbetta et al., 2008; Shulman and Corbetta, 2012 for review). The latter system is strongly lateralized, with the temporo-parietal junction in the right hemisphere constituting one of its crucial neural nodes, whereas the dorsal network is organized bilaterally, including the intraparietal sulcus and the frontal eye field of both hemispheres. The lateralized organization of the ventral attentional network conforms to behavioral results showing LVF advantages in selection of unattended targets (Evert et al., 2003; Asanowicz et al., 2012). In the two-stream

RSVP task, participants do not know exactly where and when targets will occur, thus constant monitoring of both streams is needed for successfully selecting T2, providing a typical situation of competitive processing (Desimone and Duncan, 1995). In such case, the ventral attentional system would have to be constantly engaged during performing the task (cf. Shulman and Corbetta, 2012). Because this right-lateralized network has direct access to the information from the LVF, this information may be favored in this competition, whereas RVF information has yet to be relayed through the corpus callosum, which takes more time and also may somewhat degrade the relayed percept, as would be predicted from the callosal relay model of functional lateralization (Zaidel, 1983; Moscovitch, 1986). If this scenario holds true, then the LVF advantage in T2 identification should be a function of the degree of involvement of the ventral orienting system, which might be manipulated by cueing of T2 location (cf. Shulman et al., 2010). The system is supposed to be least involved after valid cues, because then T2 would be presented directly to the focus of attention directed by the cue, moderately involved in some neutral-cue condition, and most involved after invalid cues, because then T2 would be presented at uncued location while attention is focused on the cued location (cf. Corbetta and Shulman, 2002). Recent behavioral and ERP experiments from our laboratories seem to confirm this prediction, showing the expected gradient of asymmetry across the three cue conditions in the two-stream RSVP task (in preparation).

The perceptual explanation is, on the other hand, in line with the notion of the RH's greater efficiency in initial, early visuospatial processing (Hellige and Webster, 1979; Grabowska and Nowicka, 1996). Several studies have shown that an LVF/RH advantage was observed when stimuli were perceptually degraded by manipulating parameters like exposure duration, retinal eccentricity, luminance, contrast, and blurring, even in tasks in which the LH is supposed to be dominant and, accordingly, a RVF advantage is usually observed (see Christman, 1989; Grabowska and Nowicka, 1996 for review). More direct evidence for this hypothesis was provided by an ERP study showing higher amplitude of N1 and P2 VEP components in the right than in the left hemisphere, recorded from occipital regions during processing of very briefly presented (30 ms) grating stimuli (Grabowska et al., 1992). The two-stream RSVP task seems to entail a rather extreme case of visibility degradation, greatly increasing demands for the perceptual system, because stimuli in this task are presented very rapidly, with short exposure duration, with retinal eccentricity, and simultaneously in both VFs. Thus, behavioral results from the two-stream RSVP task showing the LVF advantage, as well as the above-mentioned asymmetry in latency of early VEPs (Verleger et al., 2011, 2013) may be seen as conforming to the perceptual hypothesis.

CONCLUSION

The present two-stream RSVP experiments have shown that the LVF advantage in identifying rapidly presented target stimuli is neither appreciably decreased by reducing the hypothesized overload of the LH nor reversed into a RVF advantage by attempting to overload the RH. Thereby, although not entirely disproving the overload hypothesis, these results suggest as the most parsimonious explanation that the asymmetry may be related to RH superiority, plausibly both in initial perceptual processing and in attentional selection.

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Interhemispheric vs. stimulus-response spatial compatibility effects in bimanual reaction times to lateralized visual stimuli

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In the present study, we tested right- and left-handed participants in a Poffenberger paradigm with bimanual responses and hands either in an anatomical or in a left-right inverted posture. We observed a significant positive crossed-uncrossed difference (CUD) in RTs for both manual dominance groups and both response postures. These results rule out an explanation of the CUD in terms of stimulus-response spatial compatibility (SRSC) and provide convincing evidence on the important role of interhemispheric callosal transfer in bimanual responding in right- as well as left-handed individuals.

Keywords: interhemispheric transmission, stimulus-response spatial compatibility, poffenberger paradigm, crossed-uncrossed difference (CUD), corpus callosum, left handedness

INTRODUCTION

A cross-talk between the cerebral hemispheres is essential for integrating perception and motor control between the two sides of the body. The corpus callosum (CC) provides much of the interhemispheric connections enabling this integration. Poffenberger (1912) was the first to tackle this issue experimentally by using a simple reaction time (RT) paradigm to measure interhemispheric transfer time. His rationale relied on the lateralized hemispheric representation of right and left visual hemifields and the lateralized control of distal movement. According to Poffenberger's "anatomical model" when using the hand on the same side of a lateralized visual input stimulus detection and motor response can be integrated within one and the same hemisphere (*uncrossed pathway*). In contrast, when using the hand contralateral to the side of stimulus presentation detection and response must be integrated across hemispheres through the CC (*crossed pathway*). This longer route should result in a slower RT and this is what Poffenberger (1912) and many others since then have found (see for reviews Bashore, 1981; Marzi et al., 1991; Zaidel and Iacoboni, 2003). Since Poffenberger's pioneering study the RT difference between crossed and uncrossed conditions (CUD) is taken as a measure of interhemispheric transfer time (normal values about 3–4 ms). Clear evidence for this "anatomical" callosal interpretation of the CUD comes from its dramatic lengthening following surgical or genetic absence of the CC with values that show at least a 10-fold increase following total callosotomy (Zaidel and Iacoboni, 2003). However, the "anatomical" model has been criticized by various authors on several grounds (see Kinsbourne, 2003; Saron et al., 2003a,b). The criticism that we have considered in the present study is the one originally put forward by Broadbent (1974) which was inspired by the seminal experiments of Wallace (1971) on stimulus-response spatial compatibility (SRSC) effects (see also Umiltà and Nicoletti, 1990; Proctor and Vu, 2006). Broadbent argued that the CUD might be explained in terms of SRSC effects which have higher-level, cognitive instead of lower-level, anatomic determinants. It should be pointed out that in a typical SRSC task a choice rather than a simple reaction paradigm is employed and participants are to discriminate a visual stimulus randomly presented on the left or on the right by pressing a left or a right button. In one block of trials they are instructed to respond with the hand ipsilateral to the stimulus (compatible mapping condition), whereas in the other block they are instructed to respond with the hand contralateral to the stimulus (incompatible mapping condition). Performance is faster in the compatible (same stimulus and response side) compared to the incompatible (opposite stimulus and response side) conditions.

SRSC effects are typically attributed to response selection processes. More recent studies have stated that only if stimulus and response set *overlap* (Kornblum et al., 1990; Kornblum, 1992), that is, share levels of similarities, as is the case for left-right stimuli and responses, the spatial code of the stimulus produces *automatic activation* of the ipsilateral response (see also De Jong et al., 1994). In the compatible mapping condition, the automatically-activated response is identical to the one that was assigned to that stimulus by the instructions. In contrast,

with incompatible mapping the required response is the opposite of the automatically-activated one. Thus, when the stimulus is presented the ipsilateral response is automatically activated regardless of whether subjects were instructed to respond with the compatible or incompatible spatial mapping. Simultaneous with this activation is the *response identification* process which is performed through the application of a rule. In the case of compatible mapping response identification proceeds by the simplest and fastest *identity rule* (i.e., "select the response having identical value to stimulus"). Because the automatically-activated and the rule-based response are the same, and this response has been preprogrammed, it can be executed rapidly. Instead, in the case of incompatible mapping response identification is carried out through an *opposite rule* (i.e., "select the response having opposite value to stimulus"). In this case, the verification process will be delayed and response identification will take longer than compatible mapping. Moreover, since the automatically activated and the correct rule-based response differ, the first must be inhibited to avoid conflict with the second at the time of execution. The abort process needed to minimize errors constitutes a second source of delay.

The cognitive bases of SRSC effects are demonstrated when participants are required to cross their hands in that the SRSC effect reverses: responses given with the right hand pressing the left button are slower when the stimulus is on the right compared to when is on the left, while the opposite is true for the left hand. Therefore, crossing the hands in a SRSC RT task yields slower performance for the hand anatomically ipsilateral but spatially contralateral to the stimulus. This finding demonstrates that in a choice RT task, with spatially overlapping responses to visual stimuli, response alternatives are coded as a function of the spatial location of the response devices (e.g., buttons) independent from the anatomical state of the effectors. The SRSC account of the CUD was put to an experimental test independently by Anzola et al. (1977) and by Berlucchi et al. (1977) who demonstrated that in a typical Poffenberger paradigm, i.e., employing simple RT, a CUD effect is still present when participants responded with their hands crossed. When responses were executed with the left hand in the right hemispace and the right hand in the left hemispace, participants were still faster with the hand *anatomically* ipsilateral, but *spatially* contralateral, to the visual stimulus. This rules out an explanation of the CUD in terms of SRSC effects at least for simple RT while they might play an important role in choice RT paradigms (see Berlucchi et al., 1977). In a further experiment using a go-nogo paradigm Berlucchi et al. (1977) found a similar "anatomical" effect as with simple RT.

One should consider, however, that so far the evidence for an anatomical explanation of the CUD has been provided only with unimanual responses and in principle one might argue that SRSC effects might play a role with bimanual responses, a condition in which the importance of interhemispheric transfer may be minimized (for a discussion, see Di Stefano et al., 1980). Therefore, the present study investigated the presence of anatomical vs. SRSC effects in a Poffenberger paradigm with bimanual RT to lateralized stimuli. The presence of an anatomical CUD with bimanual responding would considerably strengthen the callosal relay hypothesis. In a previous study, Di Stefano et al. (1980) assessed the presence of a CUD in unilateral and bilateral key-pressing and lever-pulling conditions with hands in anatomical position. While the unilateral conditions provided significant CUD effects, when bilateral key-pressing and lever-pulling responses were employed, a reliable, albeit small, CUD was present only for key pressing (with the right hand), that is, with a distal response, while was absent for lever pulling, that is, with a proximal response. The authors explained their results by assuming that while unilateral and bilateral distal responses are produced by a lateralized motor pathway, bilateral proximal responses are dependent on a bilateral motor system which ensures a yoked movement of both limbs and therefore no interhemispheric transfer is necessary. However, an important demonstration of the role of the CC with bimanual responses in the Poffenberger paradigm comes from work of Aglioti et al. (1993) who found a lengthening of the CUD following total section or agenesis of the CC for bilaterally executed distal movements. Furthermore, more recently, an increase of the CUD was found with bimanual responses by Ouimet et al. (2010), in total callosum-sectioned patients.

As mentioned above, what is still lacking is evidence on the role of SRSC vs. callosal relay factors for the CUD in a bimanual Poffenberger paradigm. Confirming the results of Anzola et al. (1977) and Berlucchi et al. (1977) with uncrossed as well as crossed posture of the arms but using bimanual responding would provide convincing evidence on the role of interhemispheric transfer in the CUD effect. Moreover, in the present study we wanted to study the role of handedness, that is, a structural variable which might affect interhemispheric transfer. Evidence on the CUD in left-handers is not very abundant: in Marzi et al.'s (1991) meta-analysis were included five studies in left-handers with normal hand posture in writing with a total of 84 subjects and a mean CUD of +4.0 ms that is similar to that of right-handers. In contrast, analysis of four studies of left-handers with inverted hand posture with a total of 77 subjects yielded a mean CUD of −2.4 ms. This suggests that paradoxically in the latter group the crossed pathway might be faster than the uncrossed one perhaps as a result of a more efficient callosal transmission.

Finally, another aim of the present study was to investigate whether an asymmetry of the CUD, which has been found for unimanual responses (for a review see Marzi, 2010) is also present when a bimanual response is employed. Marzi et al. (1991) originally found that in the two crossed hand-hemifield conditions, the left visual field/right hand condition (LVF-RH) yielded faster RT than the right visual field/left hand condition (RVF-LH). Thus, while for the right hemisphere the time to access either hand is roughly similar (CUD = 2 ms), for the left hemisphere it takes almost three times longer to access the left than the right hand (CUD = 5.8 ms). In other words, callosal transfer from the right to the left hemisphere is faster than from the left to right. Interestingly, this asymmetry is reduced or absent in left-handers with either normal or inverted writing hand posture (Marzi, 2010).

EXPERIMENT 1

Experiment 1 essentially replicated the distal bilateral key-pressing condition of Di Stefano et al.'s (1980). Half the participants was to press with each hand the button on the ipsilateral

side of space whereas the other half pressed with each hand the button on the contralateral side, while keeping the arms crossed.

MATERIALS AND METHODS

Participants

Twenty-eight students (26 from the University of Bologna and 2 from RWTH Aachen University, 23 females and 5 males, mean age = 21, SD = 3.43) were tested individually. They were all right-handed (72/100, SD = 18.75) as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). All had normal or corrected-to-normal vision and were naïve as to the purpose of the study.

Apparatus and stimuli

The experiment was carried out in a dimly lit and noiseless room. The participants were seated facing a 17 in. screen driven by a 700 MHz PC with the head positioned in an adjustable head-and-chin rest so that the eye distance from the screen was 52 cm. Stimulus presentation and response recording were controlled by the E-Prime Version 1.1 software (www.pstnet.com; Psychology Software Tools, Inc.).

An 8 × 8 mm white fixation cross (0.9 × 0.9° of visual angle) was presented on a black background at the beginning of the experiment. The stimulus was an 18 × 18 mm (2 × 2°) light gray square presented 15° to the left or right of the fixation cross. Two button boxes were aligned with the left and right stimulus locations, respectively and connected to a PST serial response box.

Procedure

The fixation cross remained visible across the experiment and a tone signaled the start of each trial. After a 1000–1800 ms random interval the stimulus was presented for 100 ms and then followed by a 1000 ms blank during response collection. Participants were instructed to press the left and the right button *simultaneously* when the stimulus appeared on either side of the screen. Half the participants ($n = 14$) pressed the left and the right button with the left and the right index finger, respectively (*anatomical condition*). For the other half, the position of the hands was crossed at mid-forearm with respect to the response buttons. Thus, participants were instructed to press the left and the right button with the right and the left index finger, respectively (*inverted condition*). Furthermore, in the first half of the experiment, half participants had their hands crossed with left forearm placed over the right, while in the second half they switched to the opposite arrangement. The other half of participants followed the opposite order of forearm arrangements.

The location of the visual stimuli and of the response buttons were irrelevant to the task; both ipsilateral and contralateral RTs were collected on each trial. Omissions, single button presses and anticipations (key presses before or within stimulus onset) were considered errors and discarded. After a correct response, the RT of the first pressed button was displayed for 600 ms, otherwise, error messages were displayed for 1200 ms. The experiment consisted of one practice block of 20 trials followed by four experimental blocks of 100 trials each separated by a rest break. Response omissions (0.4%), unimanual responses (1.2%), responses faster than 120 ms (0.4%) and slower than 700 ms (0.2%) were not considered for statistical analysis.

RESULTS

Correct RTs[1] were submitted to a mixed ANOVA with *Hand arrangement* (anatomical vs. inverted) as between-participants and *Visual field* (Left vs. Right) and *Responding hand* (Left vs. Right) as within-participants factors. Paired sample *T*-tests were employed as *post-hoc* tests; Bonferroni correction was applied so that the *p*-level was decreased to 0.025 for the first order interactions. All main effects were far from significance. *Hand arrangement*: $F_{(1, 26)} < 1$, $p = 0.422$. *Visual Field:* $F_{(1, 26)} < 1$, $p = 0.990$; *Hand*: $F_{(1, 26)} = 2.346$, $p = 0.138$. The interaction *Visual Field* × *Hand arrangement* was not significant: $F_{(1, 26)} = 1.121$, $p = 0.229$, while, the *Hand* × *Hand Arrangement* interaction was marginally significant $F_{(1, 26)} = 4.116$, $p = 0.053$ with the right hand slightly faster (254 ms) than the left hand (261 ms) with the inverted, but not with the anatomical arrangement (left hand = 267 vs. right hand = 268 ms). Importantly, the *Visual Field* × *Hand* interaction was significant $F_{(1, 26)} = 20.532$, $p < 0.001$ witnessing the presence of an overall CUD of +2.0 ms, see **Figure 1**. When the stimulus was in the RVF the right hand responded faster than the left hand (260 vs. 265 ms) $t_{(27)} = 2.454$, $p = 0.021$ whereas, when the stimulus was in the LVF there was no difference between the hands (262 vs. 263 ms) $t_{(27)} = 0.462$, $p = 0.648$. The important finding here was that these effects were independent from hand arrangement as shown by the non-significant second order *Hand Arrangement* × *Visual Field* × *Hand* interaction $F_{(1, 26)} = 1.028$, $p = 0.320$.

Thus, by ruling out the role of SRSC, this result extended the anatomical account to a CUD obtained with bimanual responding in a population of right handers. Interestingly, the CUD was asymmetric with a significant 5 ms CUD when the stimulus was presented on the right visual field while was unreliable when stimuli were presented on the LVF (see **Figure 1**) and this is in keeping with Marzi et al.'s (1991) meta-analysis.

EXPERIMENT 2

Experiment 2 used the same bimanual RT task employed in Experiment 1 (with anatomical and crossed hands) in a group of left-handed participants.

MATERIALS AND METHODS

Participants

Twenty-eight students from the University of Bologna (11 females and 17 males, mean age = 21.15, SD = 1.97) participated in the experiment. They were all left-handed(−55/100, SD = 28.95) as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

Apparatus, Stimuli, and procedure were the same as in Experiment 1. Response omissions (0.3%), unimanual responses

[1]For both Experiment 1 and Experiment 2, the same ANOVA performed on RTs was also performed on variance. No sources of significance were observed (*Fs* < 1) indicating a similar variance associated with crossed and uncrossed hemifield-hand conditions.

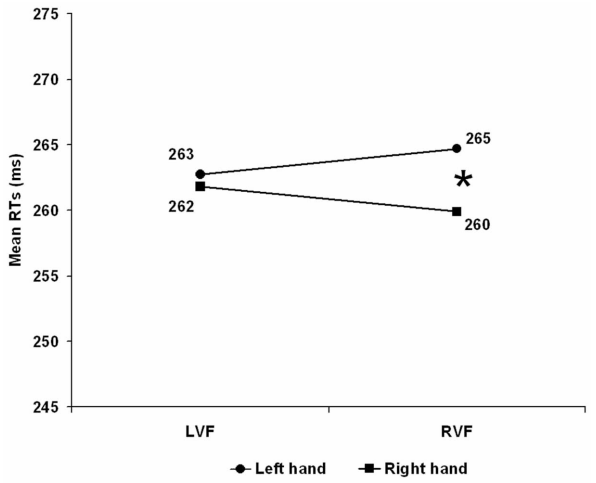


FIGURE 1 | Experiment 1: Right Handers. Mean reaction time (RT) as a function of visual hemifield of stimulus presentation and response hand. LVF, left visual field; RVF, right visual field. The asterisk indicates significant *post-hoc* test ($p < 0.025$).

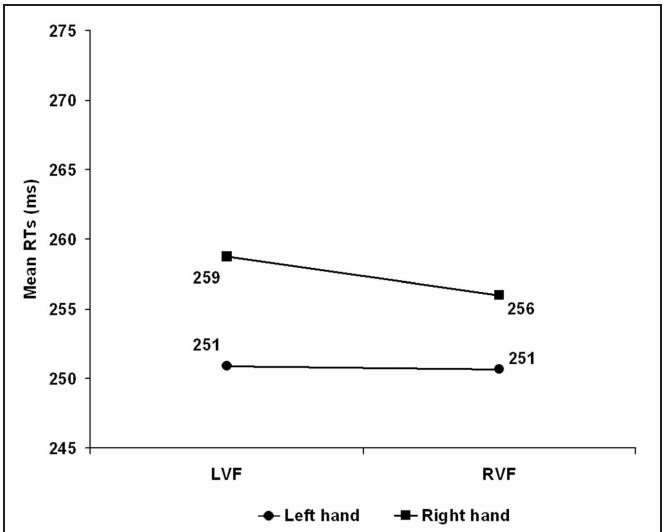


FIGURE 2 | Experiment 2: Left Handers. Mean reaction time (RT) as a function of visual hemifield of stimulus presentation and response hand. LVF, Left visual field; RVF, right visual field.

(2.2%), responses faster than 120 ms (0.8%) and slower than 700 ms (0.2%) were discarded. Correct RTs were submitted to the same mixed ANOVA as in Experiment 1.

RESULTS

The *Hand Arrangement* main effect was significant $F_{(1, 26)} = 5.749$, $p = 0.024$ with the anatomical slower than the inverted arrangement (265 vs. 243 ms). The *Visual Field* main effect was not significant (LVF = 255 vs. RVF = 253) $F_{(1, 26)} < 1$, $p = 0.376$ whereas the *Hand* main effect was significant with the dominant left hand faster (251 ms) than the right (257 ms) $F_{(1, 26)} = 20.528$, $p < 0.001$. The *Visual Field* × *Hand arrangement* interaction was just significant $F_{(1, 26)} = 4.217$, $p = 0.050$ with reliably faster RTs with inverted compared to anatomical arrangement for the LVF (243 vs. 267 ms) $t_{(26)} = 2.850$, $p = 0.008$ but not for the RVF (244 vs. 262 ms) $t_{(26)} = 1.905$, $p = 0.068$. The *Hand* × *Hand arrangement* $F_{(1, 26)} < 1$, $p = 0.574$ was not significant while, consistently with Experiment 1, the *Visual Field* × *Hand* interaction, witnessing the presence of an overall CUD of +1.5 ms, reached significance $F_{(1, 26)} = 32.458$, $p < 0.001$ with the dominant left hand faster than the right in both the LVF (251 vs. 259 ms) and the RVF (251 vs. 256 ms) but with a larger CUD in the LVF (see **Figure 2**).

More importantly, as in Experiment 1 this effect was independent from hand arrangement as demonstrated by the non-significant *Hand Arrangement* × *Visual Field* × *Hand* interaction $F_{(1, 26)} = 2.077$, $p = 0.161$.

Thus, in both right- and left-handers bimanual RTs with lateralized visual stimuli yielded a significant CUD which was not affected by spatial compatibility. This strengthens the hypothesis that anatomical factors, such as callosal transfer, are responsible for the slower responses to stimuli presented contralaterally to the responding hand.

DISCUSSION

This study has provided evidence supporting an "anatomical" explanation of the CUD effect in the Poffenberger paradigm with bimanual responding. The "anatomical" explanation posits that the CUD depends on a longer route involving callosal transmission during the crossed with respect to the uncrossed hemifield-hand condition. The crucial role of the CC has been established by behavioral studies in callosum sectioned or agenetic patients (Marzi et al., 1991; Zaidel and Iacoboni, 2003; Savazzi et al., 2007) or by a series of electrophysiological (Rugg et al., 1985; Marzi et al., 2003), transcranial magnetic stimulation (Marzi et al., 1998) and brain imaging studies (Marzi et al., 1999; Tettamanti et al., 2002; Omura et al., 2004; Weber et al., 2005; Mazerolle et al., 2008, 2010; Gawryluk et al., 2011). Moreover, a direct comparison of anatomical and spatial compatibility effects has been carried out by Anzola et al. (1977) and by Berlucchi et al. (1977) with a similar conclusion supporting the "anatomical" explanation. However, all the above studies employed a unimanual RT paradigm and in principle the relative importance of SRSC vs. anatomical effects might be different under bimanual conditions (see Di Stefano et al., 1980).

To answer this question, in the present study we employed a Poffenberger paradigm with bimanual responses and anatomical or inverted posture of the hands with respect to right and left response buttons. To ascertain the role of handedness we extended the study to a population of left-handers whose bimanual performance in a Poffenberger paradigm has never been tested and in whom the relative role of anatomical vs. spatial compatibility factors might be different from that of right-handers.

We found that in both right-handers and left-handers the crucial interaction between the CUD, as assessed by the first order Hand by Visual field interaction, and Hand arrangement was

always far from significance thus ruling out a reliable effect of inverting the anatomical hand posture. Interestingly, Experiment 1 on right-handers confirmed a CUD asymmetry that was larger in the right than the left visual field thus confirming previous findings (see Marzi et al., 1991; Marzi, 2010). This asymmetry showed a tendency to be reversed in left-handers; a result that is also in keeping with previous evidence (Marzi et al., 1991).

Two further variables need to be tested for a thorough assessment of the role of anatomical vs. SRSC factors in the study of laterality effects in simple unimanual and bimanual RT, namely gender and hand posture in writing (in left-handers). These two variables could not be tested in the present study but in principle they might influence the weight of anatomical vs. SRSC factors in explaining the CUD.

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Behavioral laterality of the brain: support for the binary construct of hemisity

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Three terms define brain behavioral laterality: hemispheric dominance identifies the cerebral hemisphere producing one's first language. Hemispheric asymmetry locates the brain side of non-language skills. A third term is needed to describe a person's binary thinking, learning, and behaving styles. Since the 1950s split-brain studies, evidence has accumulated that individuals with right or left brain behavioral orientations (RPs or LPs) exist. Originally, hemisphericity sought, but failed, to confirm the existence of such individual differences, due to its assertion that each individual lay somewhere on a gradient between competing left and right brain extremes. Recently, hemisity, a more accurate behavioral laterality context, has emerged. It posits that one's behavioral laterality is binary: i.e., inherently either right or left brain-oriented. This insight enabled the quantitative determination of right or left behavioral laterality of thousands of subjects. MRI scans of right and left brain-oriented groups revealed two neuroanatomical differences. The first was an asymmetry of an executive element in the anterior cingulate cortex (ACC). This provided hemisity both a rationale and a primary standard. RPs and LPs gave opposite answers to many behavioral preference "either-or," forced choice questions. This showed that several sex vs. hemisity traits are being conflated by society. Such was supported by the second neuroanatomical difference between the hemisity subtypes, that RPs of either sex had up to three times larger corpus callosi than LPs. Individuals of the same hemisity but opposite sex had more personality traits in common than those of the same sex but different hemisity. Although hemisity subtypes were equally represented in the general population, the process of higher education and career choice caused substantial hemisity sorting among the professions. Hemisity appears to be a valid and promising area for quantitative research of behavioral laterality.

Keywords: asymmetry, anterior cingulate cortex, cognition, right vs. left brain orientation, sex differences

INTRODUCTION

Awareness of laterality of brain function is at least as old as written history. For example, Diocles of Carystus in the 4th century BC insightfully wrote:

> *There are two brains in the head, one which gives understanding, and another which provides sense-perception. That is to say, the one which is lying on the right side is the one that perceives: with the left one, however we understand. (Lockhorst, 1985)*

However, Marc Dax was the first in modern times to observe a difference in function between the hemispheres. In 1836 he noticed that victims of injury to the left hemisphere (LH) but not to the right hemisphere (RH) could not speak (Dax, 1865). Paul Broca extended this work by additionally noting that often the dominant hand was contralateral to the language hemisphere (Broca, 1865).

HEMISPHERIC DOMINANCE vs. HEMISPHERIC ASYMMETRY

For the following century, the term "hemispheric dominance" was only used to refer to language laterality of the brain. Then, a large study by Weisenberg and McBride (1935) demonstrated RH excellence in visuospatial skills. This called for the invention of a second term, "hemispheric asymmetry," to describe the many more-recently discovered non-language differences in cerebral structure and function, most notably those revealed in "split-brain" subjects. These individuals had been created by treatment for intractable epilepsy by cutting the corpus callosum, the main cerebral connection between the hemispheres, thus limiting the spread of seizures from one side to the other (Gazzaniga et al., 1962, 1967; Sperry, 1982; Gazzaniga, 2000).

Based upon the surprisingly different responses obtained from each of these isolated hemispheres within split-brain subjects (Gazzaniga et al., 1962, 1967; Geschwind et al., 1995; Gazzaniga, 2000), it was early proposed by investigators that the right and left cerebral hemispheres are characterized by inbuilt, qualitatively different and mutually antagonistic modes of data processing, separated from interference by the major longitudinal fissure of the brain (Levy, 1969; Sperry, 1982). In this model, the LH specialized in top-down, deductive, cognitive dissection of local detail. In contrast, the RH produces a bottom-up, inductive, perceptual synthesis of global structure (Sperry, 1982; Schiffer, 1996;

Gazzaniga, 2000). This functional asymmetry context has been reinforced by known laterality differences between them. That is, there are striking differences in input to each hemisphere, differences in internal neuronal-columnar architecture, and differences in hemispheric output (Kosslyn et al., 1989, 1992; Schuz and Preissl, 1996; Hutsler and Galuske, 2003; Jager and Postma, 2003; Stephan et al., 2006) that support a local wiring on the left vs. global wiring motif on the right.

Congruent with the above local-global view is a large body of detailed evidence that the left cerebral hemisphere in most right-handed individuals manifests facilities for language (Broca, 1865), has an orientation for local detail (Robertson and Lamb, 1991), has object abstraction-identification abilities (Kosslyn, 1987), and appears to possess a hypothesis-generating, event "Interpreter" (Gazzaniga, 1989, 2000; Wolford et al., 2000). In contrast, the RH has been demonstrated to excel in global analysis (Robertson and Lamb, 1991; Proverbio et al., 1994), object localization (Kosslyn et al., 1989), facial recognition (Milner, 1968), and spatial construction (Sperry, 1968).

Among the about 90% of humans who are right-handed (Coren, 1992), language is located in the LH in about 96% of them (Knecht et al., 2000). Of the remaining about 10% of left handed individuals, some 73% of these also have language in their left cerebrum (Knecht et al., 2000). Thus, by simple arithmetic it follows that that the LH houses language ability in about 93.7% of us.

HEMISPHERICITY

It is of interest here that within this huge group of right handed, LH dominant speakers, the existence of two major human sub-populations has repeatedly been inferred (Sperry, 1968, 1982; Bogen, 1969; Levy, 1969; Bradshaw and Nettleton, 1981; Kosslyn, 1987; Robertson and Lamb, 1991; Davidson, 1992; Schiffer, 1996; Springer and Deutsch, 1998), whose characteristic thinking and behavior styles differ in a manner that appeared to mirror the putative properties of the asymmetric hemispheres. That is, in some right-handed, LH languaged individuals, putative LH traits seemed to be ascendant, to produce a "Left brain-oriented" thinking and behavioral style (Fink et al., 1996; Springer and Deutsch, 1998). Such left brain-oriented persons are currently summarized as top-down, detail-oriented, deductive, "splitters." Yet, in another equally large group of right-handed LH languaged persons, RH traits are thought to be more prominent, resulting in a contrasting "Right brain-oriented" style (Davidson and Hugdahl, 1995; Schiffer, 1996), currently viewed as bottom-up, global, inductive, "lumpers."

Thus, the original permanent assignment of the terms "hemispheric dominance" to language laterality, and "hemispheric asymmetry" to non-motor lateralities ultimately forced the creation of a third asymmetry term, that of "Hemisphericity" (Bogen, 1969; Bogen et al., 1972) in order to describe this third phenomenon, behavioral laterality style. This term was needed in order to refer to the differences in left and right brain thinking and behavioral properties within the two groups of individuals with language dominance and non-language asymmetry commonalities.

Why should hemisphericity exist? Upon what mechanism might these two thinking and behavioral styles of hemisphericity depend? Early studies of this phenomenon were doomed by misconception that hemisphericity was the result of hemispheric competition (Corbalis, 1980; Bradshaw and Nettleton, 1981; Beaumont et al., 1984). This resulted in hundreds of conflicting reports. For example, many studies found the presence of frontal EEG alpha asymmetries related to emotional states [reviews by Davidson (1984a,b, 1988)]. State-independent or trait-related individual differences in EEG asymmetries related to affective valence have also been described, [reviews by Davidson and Tomarken (1989); Davidson (1992)].

Similarly, another commonly employed measure of hemisphericity has been the predominant direction of conjugate lateral eye movements (CLEMs) in response to questions requiring reflective thought. CLEMs have been proposed as a measure of relative hemispheric activation, greater on the side contralateral to the direction of eye movement (Kinsbourne, 1972, 1974; Bakan and Strayer, 1973; Gur, 1975). Both EEG and CLEM lateralities seem related to hemispheric emotional asymmetry, but do not appear to be valid predictors of differences within normal behavior (Beaumont et al., 1984; Reine, 1991).

Further, within the formal definition of hemisphericity, attempts to keep the discipline of psychology scientific demanded each person to be located somewhere on a gradient between putative left and RH behavioral extremes. Because most subjects hesitate to mark extremes (Dawes, 2008), this impeded the development of usable quantitative methods needed to determine individual hemisphericity. After thousands of conflicting reports, the field of hemisphericity collapsed in the 1980s, primarily due to these foundational misunderstandings and this unhelpful definition, (Beaumont et al., 1984; Efron, 1990; Fink et al., 1996; Schiffer, 1996; Ornstein, 1997; Springer and Deutsch, 1998). Hemisphericity has since been called a neuromyth that was debunked in the scientific literature 25 years ago (Corbalis, 1980; Lindell and Kidd, 2011). As a result, publications have plummeted so that over the last 20 years the term hemisphericity has appeared in the title of only seven publications listed in Medline, aside from those of this author. In contrast, other aspects of brain laterality, such as handedness or language dominance, have hundreds of publications over the same period. Recently, a further nail in the coffin of hemisphericity has been supplied by the observation that no individual or group differences in lateral brain activity could be seen by functional magnetic resonance imaging (fMRI) (Nielsen et al., 2013).

HEMISITY

A quarter of a century after the "death" of hemisphericity and of the consequent loss of a valid and needed term to describe the brain behavioral laterality of individuals, a new more accurate approach to behavioral laterality term was created, called "Hemisity," (Morton and Rafto, 2010). Unlike hemisphericity, hemisity is binary; thus matching the other two binary descriptors of brain behavioral laterality: hemispheric dominance and asymmetry (**Table 1**). In this new context, an individual is inherently, unavoidably, and irreversibly either left, or

Table 1 | Three essential cerebral hemisphere laterality terms.

Hemispheric Dominance: A valid term that refers to which cerebral hemisphere houses first language production skills.
Hemispheric Asymmetry: A valid term that refers to which hemisphere produces the various non-language skills, such as facial recognition, emotion recognition, emotion production.
Hemisphericity: An obsolete term that tried to describe an individual's characteristic learning and behavioral style as being located somewhere on a gradient between right and left brain extremes.
Hemisity: A term replacing hemisity that refers to which hemisphere inherently contains an individual's unilateral executive element, the source of their characteristic learning/behavioral style. Thus, each person is inherently either left or right brain-oriented. Adding sex, the other binary identifier, produces the four major hemisity subtypes: RM, RF, LM, and LF. This situation requires rethinking of sexual characteristics, which are presently being conflated with hemisity subtype characteristics.

right brain-orientated in thinking and behavioral style, and in a manner quite unrelated to hemispheric competition. Thus, hemisity has restored a valid descriptor for the above mentioned essential third element necessary to describe brain laterality. The author entered the field in 2001 with this binary distinction, but initially published his results under the term of hemisphericity.

BIOPHYSICAL AND QUESTIONNAIRE MEASURES OF HEMISITY

In contrast to analog hemisphericity, the binary "hemisphericity" (hemisity) concept was more in alignment with the qualitatively different and mutually antagonistic modes of data processing of the opposite cerebral hemispheres, and certainly was much easier to quantify. Numerous "hemisphericity" reports were published (Morton, 2001, 2002, 2003a,b,c,d; Morton and Rafto, 2006). This series was continued by publication of additional "hemisity" reports (Morton and Rafto, 2010; Morton, 2012; Morton et al., 2014).

First, four independent biophysical methods were devised to separate right and left brain- oriented persons (RPs and LPs). Each of these showed a remarkable consistency in dividing large groups of individual into nearly the same groups of LPs and RPs. Based upon the identity of these hemisity subgroups, ultimately four "either-or" forced choice preference type questionnaires were created whose applications also divided a large starting group into the same RP and LP hemisity subgroups. These biophysical and derivative questionnaire methods are briefly described next.

DICHOTIC DEAFNESS TASK

Morton (2001) reported that normal subjects could be segregated into two groups on the basis of the Dichotic Deafness Test, a dichotic listening task involving the simultaneous presentation of non-matching pairs of consonant-vowel syllables (CV). "Dichotically hearing" subjects reported more than 40% of the syllables presented to their minor (left) ear compared to their major (right) ear, while "dichotically deaf" subjects reported less than 40% of the CV syllables presented to their minor ear. Forty percent was an arbitrary bootstrapping value empirically found to provide optimal separation of the two groups. Morton (2002) found that dichotically hearing subjects affirmed predominantly right hemisphericity items on Zenhausern's Preference Questionnaire (Zenhausern, 1978), while dichotically deaf subject showed a left brain orientation.

POLARITY QUESTIONNAIRE

Morton (2002) described the development of a new hemisity questionnaire, The Polarity Questionnaire, the items of which were chosen for their ability to differentiate groups of subjects divided on a priori grounds into left and right hemisity groups. Grouping into dichotically hearing (right brained) and dichotically deaf (left brained) groups of subjects, defined by the Dichotic Deafness Test, showed a very strong correlation with the Polarity Questionnaire ($r = 0.51$, $p < 0.001$). This correlation was twice the magnitude of the correlation between the Dichotic Deafness Test and Zenhausern's Preference Questionnaire (Zenhausern, 1978). Only 30% of the Zenhausern's Preference Questionnaire items, vs. 90% of the Polarity Questionnaire items, were significantly correlated with Dichotic Deafness Test grouping. A low correlation between the Polarity Questionnaire and Zenhausern's Preference Questionnaire was also noted by McElroy et al. (2012) andby Morton (2012).

MIRROR TRACING TASK

Morton (2003a) had right handed subjects trace the outline of a five-pointed star as quickly as possible with either hand, using only a mirror to guide manual circumscription. Faster mirror tracing with one hand was regarded as an indication of preference for the use of the contralateral hemisphere. In the total sample of subjects, mirror tracing asymmetry was not significantly correlated with the Dichotic Deafness Test, Zenhausern's Preference Questionnaire, or the Polarity Questionnaire. However, when subjects identified as having left brain affect by use of the Affective Laterality Test (Schiffer, 1997) were removed, robust correlations between mirror tracing asymmetry and the other three hemisity measures were observed. In the Affective Laterality Test, the hemisphere which is more responsive to emotionally-evocative pictures is determined. This is done by having subjects view pictures while wearing goggles which restrict vision to the periphery (viewing with the nasal portion of the retina) by occluding the inner two thirds of each lens, thus allowing viewing by only one hemifield of one eye at a time. Subjects are asked to judge which viewing eye was associated with larger initial emotional responses to the pictures. The validity of this approach was confirmed (Schiffer et al., 2007). When the hemisity outcomes on the mirror tracing test were reversed or "phase corrected" for subjects with left brain affect (greater emotional responses to pictures viewed with the nasal portion of the right eye) and these data were included in the analysis, even larger correlations with the other three hemisity measures were evident (Morton, 2003a).

BEST HAND TASK

Extending a line bisection instrument of Schenkenberg et al. (1980), Morton (2003b) had subjects draw a line through the estimated midpoint of a set of lines of varying lengths with each hand. Midpoint estimates for each hand of an individual showed excellent repeatability and stability. When the midpoint estimates of opposite hands were compared, characteristic and often large individual differences between the accuracy of each hands to bisect the lines were observed.

Of the 412 subjects studied, 75% fell into two of the four line-bisection response categories based on the more accurate hand (*r* or *l*) and whether it crossed over the other hand to mark (c) or it did not cross over, but marked on the same (s) side as the other hand. That is, the rs category = 45% and *lc* = 30%. Most of rs-category subjects uncorrected for handedness or left-handed writing grasp were classified as left brained by the Polarity Questionnaire. Conversely, most of the subjects in the *lc*-category were classified as right brained by the Polarity Questionnaire.

For the two smaller categories, the results were somewhat more complicated. Of the 10% of the total sample who fell into the rc-category, the males were right brained (8%), while the females were left brained (2%). Of the 15% of the total sample who fell into the ls-category, those with right brain affect on the Affective Laterality Test were right brained, as determined by the Polarity Questionnaire (10%), whereas those with left brain affect had left hemisity (5%). Thus, hemisity as determined by phase-corrected line-bisection results was also strongly associated with hemisity, as determined by phase-corrected mirror tracing results, the Dichotic Deafness Test, and Zenhausern's Preference Questionnaire.

ASYMMETRY QUESTIONNAIRE

Morton (2003c) developed another questionnaire measure of hemisity, the Asymmetry Questionnaire, which consists of 15 paired statements. Within each pair, one statement exemplified a left brained characteristic while the other reflected a right brained characteristic. The Asymmetry Questionnaire was found to have strong and significant correlations with two other hemisity questionnaires, the Polarity Questionnaire and Zenhausern's Preference Questionnaire, as well as three biophysical hemisity measures, the Dichotic Deafness Test, phase-corrected mirror tracing, and phase-corrected Best Hand Test.

BINARY QUESTIONNAIRE AND HEMISITY QUESTIONNAIRE

Recently the Binary Questionnaire and the Hemisity Questionnaires have also been developed and utilized (Morton, 2012). As shown in **Table 2**, these were of comparable quality to the Polarity and Asymmetry Questionnaires. As may be seen, all four of these questionnaires were superior to the earlier hemisphericity standard, the Zenhauser's Preference Questionnaire (1978).

MRI STUDIES OF NEUROANATOMICAL DIFFERENCES BETWEEN RPs AND LPs

The above new methods enabled the accurate characterization the hemisity subtype of hundreds of subjects (Morton, 2003d). This enabled MRI studies to be carried out seeking brain structural differences between LPs and RPs. Two neuroanatomical differences were found. The first was the observation that the corpus callosum midline cross sectional area of RPs was up to three times larger than that of the LPs (Morton and Rafto, 2006). The implications of this discovery will be discussed later. Second, it was observed that in 146 of 149 cases (98%) the subject's bilateral anterior cingulate cortex (ACC) in Areas 24 and 24′ was up to 50% larger on the right side for RPs, while for the LPs it was up to 50% larger on the left (Morton and Rafto, 2010), **Figure 1**. This result motivated the transformation of this 3 min MRI procedure into the primary standard for the determination of individual hemisity subtype, as follows:

MRI ASSESSMENT OF HEMISITY (PRIMARY STANDARD)

MRI assessments (Morton and Rafto, 2010) were obtained employing a General Electric Signa 1.5 Tesla MRI instrument. A midsagittal plane setup calibration protocol was run for 3 min to image 5 mm thick slices from the midline plane and two adjoining sagittal planes 6 mm on either side. Whole-head photographic

Table 2 | Overall correlations and reliability of preference questionnaire scores with predetermined subject hemisity subtype.

Preference questionnaires (fast, easy) vs. biophysical methods (slow, difficult)	*r* (Pearsons)	*p*	*n*	% yield	alpha Cron-bach's
CORRELATIONS OF MRI PRE-ASSIGNED HEMISITY SUBTYPES WITH					
Zenhausern's preference quest-naire	0.24	0.008	119	35*	0.37
Polarity questionnaire	0.57	0.000	132	82	0.57
Asymmetry questionnaire	0.48	0.000	111	60	0.64
Binary questionnaire	0.43	0.000	112	30	0.66
Hemisity questionnaire	0.53	0.000	79	48	0.65
Best hand test (R − L)	0.37	0.000	143		
Mirror tracing test (R/L)	0.50	0.000	116		
Dichotic deafness test (R − L/R + L)	0.34	0.000	109		
vgACC laterality determined by MRI	0.93	0.000	149		

**= % yield refers to the percentage of questionnaire statements that were significantly associated with subject neuroanatomical hemisity. Pre-assigned hemisity subtype = direction of asymmetry of the ventral gyrus of the anterior cingulate cortex.*

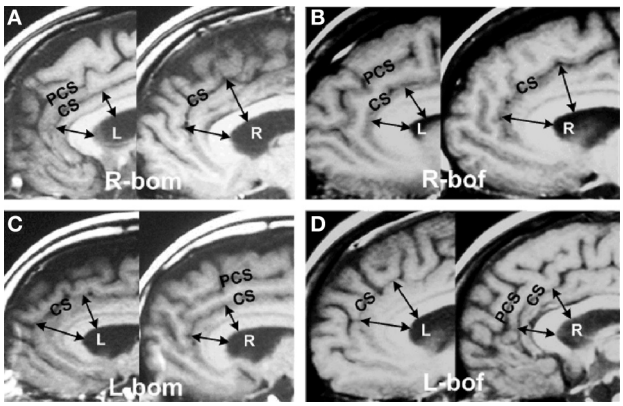


FIGURE 1 | Asymmetries in the anterior cingulate cortex. Example of MRI sagittal images taken from 149 hemisity-calibrated subjects. **(A)** Right brain-oriented male (R-bom, RM). **(B)** Right brain-oriented female (R-bof, RF). **(C)** Left brain-oriented male (L-bom, LM). **(D)** Left brain-oriented female (L-bof, LF). Pairs of arrows reaching from the lower surface of the central white corpus callosum (CC) to the cingulate sulcus (CS) illustrate four measurements made for each subject. CC thickness was the same on images from either side. PCS refers to the paracingulate sulcus. Note that the arrow lengths are longer on the right side for RPs and left side for LPs. From Morton and Rafto (2010).

images were prepared from these three planes. These three exposures were printed on a single film sheet for each subject. This procedure enabled both cortical walls on either side of the midline fissure to be visualized and measured, thus allowing sub-element lateralities of the ACC to be evaluated directly from the film. At two ACC sites on each side of the brain, one in Area 24 and the other at Area 24′ (Vogt et al., 1995), estimations of the relative thickness of the ventral gyri (vgACC) there were made. This abbreviation and these four ACC locations within Areas 24 and 24′ are not to be confused with the more frontal ventral region of the perigenual ACC. The vgACC locations where these relative thickness estimations were made are illustrated by the arrows in **Figure 1**.

Two lines were extended outward perpendicularly from the inner edge of the CC, ending in one case at a more frontal point in Area 24 and in the other at a more dorsal point in Area 24′. Both points were in the plane of the cingulate sulcus and arbitrarily selected, based upon the sites in the region giving the largest vgACC thickness for each brain side involved. The average of these two lateral relative thickness estimates from the vgACC of each side were then used to determine upon which side of each subject's brain the vgACC was thicker. This can be recognized by noting that the arrows are longer on the RH for RPs and on the left for LPs.

CALIBRATION OF EARLIER HEMISITY METHODS AGAINST THE MRI PRIMARY STANDARD

Asymmetry of the ventral gyri of the ACC was significantly correlated with hemisity as determined by the Asymmetry Questionnaire (Morton, 2003c), the Polarity Questionnaire and Zenhausern's Preference Questionnaire (Zenhausern, 1978; Morton, 2002), the Dichotic Deafness Test (Morton, 2001, 2002), the Best Hand Test (Morton, 2003b), the Phased Mirror Tracing Test (Morton, 2003a), as well as two new hemisity questionnaires, the Binary Questionnaire and the Hemisity Questionnaire (Morton, 2012). The categorical associations of each of these methods of determining hemisity with each other and with asymmetry of the vgACC were highly significant (Morton and Rafto, 2010). The correlations among continuous measures of asymmetry derived from each of these methods were also significant. All nine hemisity measures had high loadings on the first factor, suggesting an underlying dimension of hemisity accounting for the relationships among these nine measures. The correlations between these hemisity instruments may be seen in **Table 2**.

That the anatomical primary standard for hemisity was found to validate the previous secondary instruments developed to assess hemisity was gratifying because some of them were based upon possibly questionable assumptions. For example, in the Dichotic Deafness Test (Morton, 2001), it was necessary to make arbitrary decisions as to where to draw cutoff lines that defined dichotic deafness. In the Phased Mirror Tracing Method (Morton, 2003a) it was necessary to assess the subjects as to which was the more emotional side of their brain. This assessment was based upon the examiner's interpretation of the subjective judgment of the subject in response to peripheral presentation of pictures containing emotion-invoking content. In the Best Hand Task (Morton, 2003b), a certain segment of the population required redefinition of handedness and the interpretation of the sometimes-difficult assessment of pen grasp hand posture. It is paradoxical that it was necessary to develop these secondary methods first in order to calibrate the hemisity of a sufficiently large group of subjects even to begin to search for and recognize actual brain structural differences between left and right brain-oriented individuals.

However, since the previous hemisity procedures were well correlated with the primary anatomical standard, it would appear reasonable they could continue to be used in combination as secondary standards. When five of these six were used the combined outcome for the 149 subjects was 146/149 (98%) correct for hemisity subtype identity. For the 111 subjects assessed by all six secondary methods, the accuracy rose to 99%. Yet, no single secondary method can be used to absolutely identify subject hemisity, each being correct only about 80% of the time. It would appear that, the combined use of at least three or four of the five most accurate questionnaires of **Table 2**, would allow for rapid, fairly accurate measurement of the hemisity of individuals. In sufficiently large populations, this can be reduced to two hemisity questionnaires, as described later.

NEUROANATOMICAL BASIS OF HEMISITY

Coincidentally in terms of the hemisity MRI findings of ACC laterality, much evidence supports the ACC being a major structural element of the brain's executive system. Remarkably, this cortical element of the ancient limbic brain region (Roxo et al., 2011), including interconnecting integrative loops (Alexander et al., 1986) between prefrontal, striatal, thalamic, and other

limbic areas (Bonelli and Cummings, 2007) has repeatedly been shown to be involved in executive type activities. These include: decision making (Kennerly et al., 2006), error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting (Wang et al., 2005), response to pain and production of emotion: (Vogt, 2005), verbal and non-verbal executive tasks activity (Fornito et al., 2004), conflict monitoring and adjustments in control (Kerns et al., 2004), rapid processing of gains and losses (Gehring and Willoughby, 2002), interfacing between motor control, drive, and cognition (Paus, 2001), episodic memory retrieval (Herrmann et al., 2001) and the initiation and motivation of goal directed behavior (Devinsky et al., 1995).

Some ACC activities appear directly relevant to hemisity differences in behavioral styles. These include its participation in temperament (Whittle et al., 2008), reward and social learning (Behrens et al., 2008), expectancy and social rejection, Somerville et al. (2006), self-reflection (Johnson et al., 2006), personality (Pujol et al., 2002), will and addiction (Peoples, 2002). Even though psychoanalytic concepts were originally not intended to correspond to neuroanatomical structures, it can be noted that the ACC seems to mediate a number of different cognitive functions formerly subsumed under Freud's central element of control, the Ego. It certainly has the resources to implement the many behavioral differences between hemisity subtypes.

What is fascinating in terms of the hemisity story, is that not only does the ACC house a major brain executive element, but also that its two sides, separated by the cerebral midline fissure, are highly asymmetric. There are at least 10 reports of ACC structural asymmetries, especially in Areas 24, and 24′ which varied in an individually idiosyncratic manner, (Vogt et al., 1995; Paus et al., 1996a,b; Hutsler et al., 1998; Ide et al., 1999; Yucel et al., 2001; Pujol et al., 2002; Fornito et al., 2006, 2008; Huster et al., 2007; Palomero-Gallagher et al., 2008). Many of these reports mentioned efforts to identify behavioral consequences of these identified asymmetries, interestingly including their possible relationship to executive function, e.g., Pujol et al. (2002). However, these efforts lacked the unifying concept of hemisity.

Might this laterality of the ACC executive element provide a direct link to a subject's hemisity, thus supporting the observed relationship between the two? Indeed, it is here asserted that the discovery of the congruity of the larger side of the ACC with hemisity subtype has actually provided the missing mechanism to account for the existence of hemisity and for the differences between LPs and RPs. Further, such an "either-or" laterality context is consistent with the logic that there can be only one "Bottom-line," "The buck stops here" executive element in any successful institutional organization, including the mammalian brain, which is completely bilateral, except for the pineal gland. Although, Descartes (1637) was logically compelled to assert this endocrine organ to be the executive "Seat of the Soul," now, it rather appears that the executive system must be unilateral. That is, hemisity must result because an executive element, embedded in the local specialized (top-down, important details) environment of the LH, will inevitably have a different perspective than one imbedded within that of the right (bottom-up, global perspective).

Thus, the existence of major asymmetries in the ACC supports the hypothesis of the possible existence of a unilateral executive element. This idea is not new. When he learned that the bilateral ACC was the probable site of the executive system, Crick (1994) was led rhetorically to ask: "Could there be two centers of the Will?" (Sejnowski, 2004). In a "Postscript on the Will" within his book "The Astonishing Hypothesis," (1994), Crick states that he and Antonio Damasio arrived at the same negative answer to this question by noting about the ACC that the "region on one side projects strongly to the corpus striatum (an important part of the motor system) on both sides of the brain, which is what you might expect from a single Will." Parenthetically, neither their use of the term Will, nor the use of the term Executive System here were intended to invoke the idea of a decisional homunculus, but rather of a preconscious early response system (Libet, 1982) continually acting to optimize the survival of the organism.

BEHAVIORAL DIFFERENCES BETWEEN RIGHT AND LEFT HEMISITY SUBTYPES

With the ability to accurately determine the right or left brain individual hemisity subtype identity in hand, it became possible to answer some pressing questions: do these biophysically identified right and left hemisity subtype individuals differ significantly in their behavioral preferences? And if so, specifically how? Morton (2012) studied the behavioral responses of 150 subjects whose hemisity had previously been calibrated by MRI. He used five MRI-calibrated preference questionnaires, two of which were new. Right and left brain-oriented subjects selected opposite answers ($p > 0.05$) for 47 of 107 "either-or," forced choice type preference questionnaire items. Removing overlaps resulted in 30 hemisity subtype preference differences (**Table 3**). These differences could be subdivided into five areas: (1) in logical orientation, (2) in type of consciousness, (3) in fear level and sensitivity, (4) in social-professional orientation, and (5) in pair bonding-spousal dominance style.

The following is an interpretation of 30 hemisity differences found: regarding *Logical Orientation,* LPs tended to be top-down, detail oriented, and deductive vs. RPs who were more bottom-up, big picture, and inductive. Regarding *Type of Consciousness*, LPs tended to be more verbal, dependent upon abstract reasoning, and oriented to find differences between objects vs. RPs who where more visual, dependent upon concrete reasoning, and able to find commonalties between objects. As to *Fear Level and Sensitivity,* LPs were more sensitive, taciturn, emotion-avoiding and defensive (implying a thinner barrier to fear-invoking subconscious material), while RPs were more intense, bold, talkative, emotion-embracing, and invasive. For *Social and Professional Orientation*, LPs were more independent, avoidant, private, and competitive, while the RPs were more orderly, responsible, open, and cooperative. In terms of *Pair Bonding Style and Spousal Dominance,* LPs were the less dominant spouse, who needed separateness, quietness, seeking to avoid emotionality with logic, spouse assisting, and initiator of the details of family endeavors early in the day. In contrast RPs were the more dominant spouse, needing closeness and reassurance of the other's fidelity

Table 3 | Thirty binary behavioral correlates of hemisity.

Left brain-oriented persons	Right brain-oriented persons
LOGICAL ORIENTATION	
Analytical (stays within the limits of the data)	Sees the big picture (projects beyond data, predicts)
Uses logic to convert objects to literal concepts	Imagines, converts concepts to contexts or metaphors
Decisions based on objective facts	Decisions based on feelings, intuition
Uses a serious approach to solving problems	Use a playful approach to solving problems
Prefers to maintain and use good old solutions	Would rather find better new solutions
TYPE OF CONSCIOUSNESS	
Daydreams are not vivid	Has vivid daydreams
Doesn't often remember dreams	Remembers dreams often
Thinking often consists of words	Thinking often consists of mental pictures or images
Can easily concentrate on many things at once	Tends to concentrate on one thing in depth at a time
Comfortable and productive with chaos	Slowed by disorder and disorganization
Often thinking tends to ignore surroundings	Observant and in touch with surroundings
Often an early morning person	Often a late night person
FEAR LEVEL AND SENSITIVITY	
Conservative, cautious	Innovative, bold
Sensitive in relating to others	Intense in relating to others
Tend to avoid talking about emotional feelings	Often talks about own and others feelings of emotion
Suppresses emotions as overwhelming	Seeks to experience and express emotions more deeply
Would self-medicate with depressants	Would self-medicate with stimulants
SOCIAL AND PROFESSIONAL ORIENTATION	
Does not read other people's mind very well	Good at knowing what others are thinking
Thinks-listens quietly, keeps talk to minimum	Thinks-listens interactively, talks a lot
Independent, hidden, private, and indirect	Interdependent, open, public, and direct
Does not praise others nor work for praise	Praises others and works for praise
Avoids seeking evaluation by others	Seeks frank feedback from others
Usually tries to avoid taking the blame	Tends to take the blame, blames self, or apologizes
PAIR-BONDING AND SPOUSAL DOMINANCE STYLE	
Tolerates mate defiance in private	Finds it difficult to tolerate mate defiance in private
After an upset with spouse, needs to be alone	After upset with spouse, needs closeness and to talk
Needs little physical contact with mate	Needs a lot of physical contact with mate
Tends not to be very romantic or sentimental	Tends to be very romantic and sentimental
Prefers monthly large reassurances of love	Likes daily small assurances of mate's love
Often feels mate talks too much	Feels my mate doesn't talk or listen enough
Lenient parent, kids tend to defy	Strict, kids obey and work for approval

and support while being intuitive and highly directive, ending the day by reviewing the big picture survival status of the family and making plans for the next day.

It is ironic that many of these behavioral preference differences parallel some, but not all, of the putative differences between the right and left brainers popular in folk hemisphericity (Springer and Deutsch, 1998), such as detailer vs. globalist, analytical vs. synthetic, words vs. images, abstract vs. concrete (L vs. R, here). However, many more differences were revealed, most of which as yet have no recognized brain basis, for example fear vs. confidence, or morning vs. evening, quiet vs. talkative. Perhaps the use of hemisity to identify individuals with those traits may assist in identification of their underlying brain mechanism.

CORPUS CALLOSAL SIZE, HEMISITY, AND SEXUAL STEREOTYPING

As mentioned, the cross-sectional area of the midline of the corpus callosum (CCA) was found to be significantly smaller in LPs than in RPs, and to be unrelated to sex or handedness (Morton and Rafto, 2006). These observations, illustrated in **Figure 2**, have had several ramifications. To begin with, if the executive element of the anterior cingulate was in the same hemisphere as language, as is the case for most LPs, there would be less need for transcallosal communication than if the executive element was located in the opposite non-language hemisphere. Thus, the CCA in LPs would be predicted to be smaller than in RPs, as observed.

Further, hemisity behavioral outcomes contradict several commonly held beliefs about sex and the brain: first, the hemisity results lay bare the underlying basis of the previous controversy about gender and laterality. The confusion occurred because in all earlier CCA studies, the hemisity of the subjects was unknown. This caused an unwitting confounding of the results for subjects sorted only by sex or handedness with hemisity, a major factor influencing CCA (Morton and Rafto, 2006). This error brings into question the common view that the male brain is more specialized due to its higher laterality (McGlone, 1980). Rather, the CCA data strongly suggest that it is the left brain-oriented individuals of either sex who are more lateralized as a class than males are. Correspondingly, right brain individuals of either sex are less lateralized and more broadly generalized as a class than females are, thus contradicting another sexual stereotype.

Second, these findings appear to end the controversy about which sex has the larger corpus callosum (Luders et al., 2003). There was no significant difference between the two sexes in either their mean CCA, its size range, or in the IQ of the subjects (Morton and Rafto, 2006). Rather, the two largest CCAs of individuals from among our 113 subjects were possessed by a right brained female and by a right brain male (10.1 and 9.2 cm^2, respectively). Conversely, the two smallest CCAs were 4.8 cm^2 for a left brained male and 4.5 cm^2 for a left brained female. All four of these individuals held doctoral degrees and professorial status.

Third, lack of awareness that hemisity contributes to CCA makes it probable that the European studies reporting mean CCAs for males to be larger (Clarke et al., 1989) and American–Australian studies, showing larger female mean CCAs (Holloway et al., 1993) were both correct. Their disagreements could well

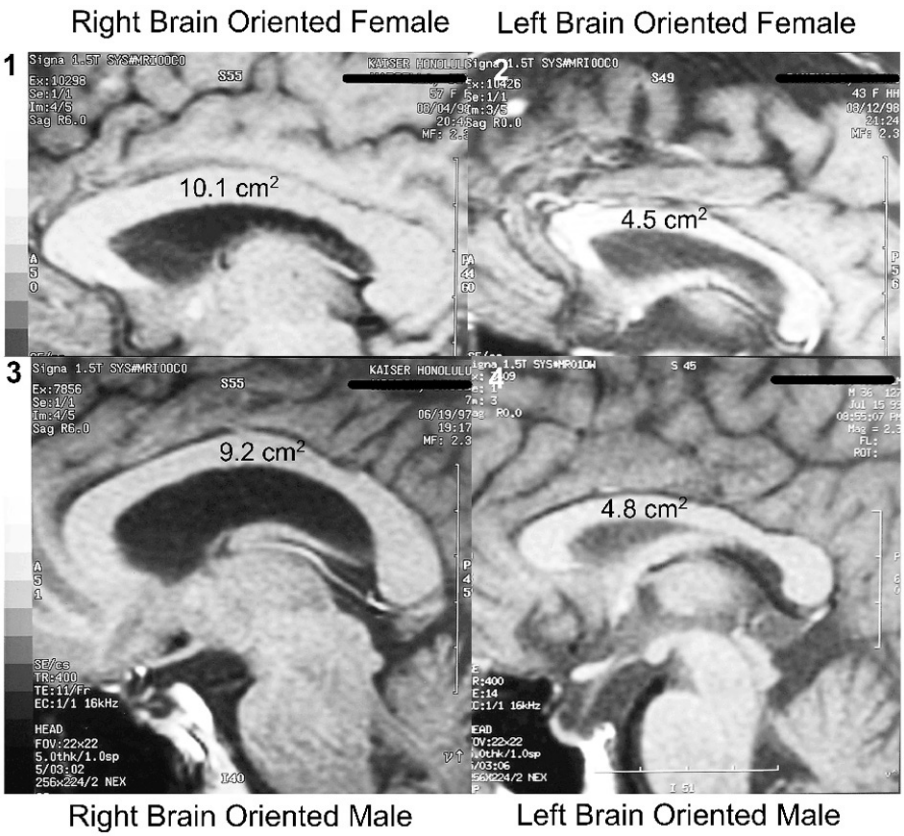


FIGURE 2 | Hemisity vs. sex: size range of corpus callosal areas. Largest CCAs of the subject group ($n = 113$): **(1)** Right brain-oriented female, 10.1 cm^2. **(3)** Right brain-oriented male, CCA 9.2 cm^2. Smallest CCAs: **(2)** Left brain-oriented female, 4.5 cm^2. **(4)** Left brain-oriented-male, 4.8 cm^2. From Morton and Rafto (2006).

be based upon regional population differences in hemisity, an important but uninvestigated topic.

Fourth, it is becoming clear that members of either sex with the same hemisity have more behavioral traits in common than do same sex individuals of the opposite hemisity. This is strongly supported by data from the MRI calibrated preference questionnaires (Morton, 2002, 2003c, 2012). Thus, it would appear that several hemisity traits are presently being misidentified as male or female sex traits. That is, men in general do not "hide in their caves of silence" (Tannen, 1990; Gray, 1992). In fact, in contrast to their right brain counterpart, left brain-oriented females are every bit as "private" as left brain-oriented males (Morton, 2002, 2003c, 2012). Similarly, females do not always "rule the roost." It is the right brain-oriented person who tends to dominate the nuclear family, be they male or female (Morton, 2002, 2003c, 2012). Because of the newness of hemisity and its new behavioral distinctions, sex traits have never been studied together with hemisity traits. Books such as John Gray's "Men are from Mars, Women are from Venus" (1992) appear to fit perfectly for about half the population (∼60%), that is, for the RFs and LMs. The other half (∼40%) say it is totally alien to them. However, if the pronouns are reversed from "him" to "her" and vice versa in the book, then the other half of the population (RMs and LFs) strongly identify with it (Morton, unpublished). So it appears not to be a description of sexual differences but rather of hemisity differences. Thus, the recognition of the quantifiable existence of hemisity can bring new clarity to human behavior.

HEMISITY DISTRIBUTIONS AND HEMISITY SORTING WITHIN POPULATIONS

Morton (2003d) investigated the distribution of hemisity subtypes within the general population. It was proposed (Morton, 2003d) that in an unsorted population not only would the numbers of male and females be equal, but that the numbers of RPs and LPs would also be similar. It was hypothesized that hemisity sorting in populations would only occur after admission into a school or an organization where entrance was competitive and selective. In the US, this typically first occurs at the university level because in essentially all public elementary, high schools, and even some community colleges, essentially no applicants are excluded and all must complete a similar general core curriculum in order to graduate.

Morton et al. (2014), using the Best Hand Test (Morton, 2003b) and the Polarity Questionnaire (Morton, 2002), measured the hemisity of 1049 public high school upper classmen from Hawaii and Utah. As predicted, in this sample there were similar

numbers males ($n = 522$) and females ($n = 527$), and of right ($n = 526$) and left ($n = 523$) brain-oriented individuals. There were reciprocal complementary relationships between right males (RMs, 39%, $n = 206$) and left females (LFs, 40%, $n = 210$), and correspondingly among left males (LMs, 61%, $n = 316$) and right females (RFs, 60%, $n = 317$), thus confirming the non-sorting hypothesis. This suggests that females are slightly enriched in RPs and males are with LPs, and therefore that the average CCA of females should be slightly greater than of males. However, these differences do not appear to obviate the four generalities of the preceding section.

The equalities of hemisity within the general population were lost among 228 competitively selected college freshmen, 57% of whom now showed left hemisity. Students in more specialized upper- division classes (Morton, 2003d) showed an increased range of hemisity distributions, from 35% left brained individuals in a civil engineering seminar to 68% left brained persons in a home economics course.

Even more pronounced hemisity distribution differences were found in university representatives of 17 different professions, ranging from only 21% left brained among astronomers and 33% left brained among architecture professors, to 83% among biochemistry professors and 86% among microbiology professors (Morton, 2003d). Professional librarians ($n = 15$) were predominantly left-brained (73% LPs), while academically trained musicians ($n = 91$) including concert pianists ($n = 47$) were predominantly right-brained (32% LPs) (Morton et al., 2014).

Within professional groups there were differences related to area of specialization. For example, among practicing civil engineers, only 39% of design civil engineers were left brained, compared to 74% of construction civil engineers. Morton (2003d) suggested that individuals in primarily "top-down" professions working at structural levels that are subdivisible, such as microbiologists, biochemists, and particle physicists, were more left brained. In contrast, those in more "bottom-up" macroscopic or gestalt-oriented professions such as architecture, civil engineering design, and astronomy, tended to be more right brained. Thus, as it may be seen, hemisity appears to play a profound role in career development.

An explanation has been proposed to account for the sorting of hemisity in higher education and career selection (Morton, 2003d). That is, sorting occurred as the result of RPs and LPs doing what they liked best. Topics at which each excelled relative to the other resulted in one hemisity subclass doing well or poorly compared to the other. Rewards from success, difficulty, or failure shaped individual opinion of the liking or dislike of specific topics. This led to the selection of topics bringing personal success and to the avoidance of those bringing failure. Thus, in general, it appears that one ends up being an architect or microbiologist simply by doing what one enjoys most.

Although both the Best Hand Test (Morton, 2003b) and the Polarity Questionnaire (Morton, 2002) were used in the above population studies, the viability of using the more easily administered Polarity Questionnaire alone to determine the hemisity of large groups was considered by comparing its outcomes here with those of the Best Hand Test alone (Morton, 2003b). For a high school population ($n = 703$), the outcomes of the two methods differed in only 5.6% of cases. Further, the Polarity Questionnaire was able to assess the hemisity of the 10.4% individuals whose Best Hand Test results were indeterminate. This supported the idea that, not only are the two measures complimentary, but also that perhaps future studies using the Polarity Questionnaire alone, or in combination with one or more of the other calibrated hemisity questionnaires might be acceptably accurate for the estimation of hemisity of large English speaking populations. However, the extreme outcome sensitivity to wording of Polarity Questionnaire statements (Morton, 2002, 2003c) suggests that great care must be taken in its translation into other languages and cultures. In contrast, biophysical hemisity methods, such as the Best Hand Test, while much more demanding to assess, appear to be language and culture independent.

Because the grading of the Best Hand Test, a research instrument, is complex, technical, and time consuming, it is not practical for use in general hemisity studies. As indicated above, similar results are easily obtained by the Polarity Questionnaire. Further, it has been shown that combined use of the Polarity Questionnaire with the three other rapid binary hemisity questionnaires that have been developed: the Asymmetry Questionnaire (Morton, 2003c), the Binary Questionnaire (Morton, 2012), and the Hemisity Questionnaire (Morton, 2012), enhances the 80% certainty of the hemisity subtype result of a single questionnaire to about 95% for combined use **(Table 2.)** Each questionnaire takes only a few minutes to administer and grade.

CONCLUSIONS

Six useful conclusions are among many that can be derived from this review of hemisity: (1) Research now supports the view that the existence of hemisity is inevitable, due to the unilateral nature of a structural element of the executive system. (2) Quantitative methods have been developed to make it possible to assess any person in terms of their probable right or left brain orientation. (3) A primary standard has been discovered that enables the absolute hemisity of an individual to be determined, based upon anatomical landmarks within the brain. (4) A number of the many "either-or" traits that separate the cognitive and behavioral styles of RPs and LPs have been identified, most of which as yet have no known ties to brain asymmetry. (5) Methods now exist which can determine the average hemisity of groups with considerable sensitivity. (6) The recognition of the quantifiable existence of hemisity as a second dyadic personal identifier after sex can bring new clarity to human behavior.

The neuroanatomical differences between left- and right-brain oriented individuals raise the question of how these features develop. Correlating parent and offspring hemisity types might provide first insights into the development of this phenomenon. However, extensive genetic research will most likely be necessary to fully unravel the development and implications of hemisity.

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Lateralized difference in tympanic membrane temperature: emotion and hemispheric activity

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We review literature examining relationships between tympanic membrane temperature (TMT), affective/motivational orientation, and hemispheric activity. Lateralized differences in TMT might enable real-time monitoring of hemispheric activity in real-world conditions, and could serve as a corroborating marker of mental illnesses associated with specific affective dysregulation. We support the proposal that TMT holds potential for broadly indexing lateralized brain physiology during tasks demanding the processing and representation of emotional and/or motivational states, and for predicting trait-related affective/motivational orientations. The precise nature of the relationship between TMT and brain physiology, however, remains elusive. Indeed the limited extant research has sampled different participant populations and employed largely different procedures and measures, making for seemingly discrepant findings and implications. We propose, however, that many of these discrepancies can be resolved by considering how emotional states map onto motivational systems, and further examining how validated methods for inducing lateralized brain activity might affect TMT.

Keywords: tympanic membrane temperature, motivational orientation, cortical asymmetry, lateralization, mood, emotion, hemispheric asymmetry

INTRODUCTION

The development of techniques allowing examination of brain activity in "real-time" has enabled great strides to be made in the field of behavioral neuroscience generally, and in determining the cortical substrates of emotion and motivational orientation specifically. Electroencephalography and functional imaging have indicated broad differences in hemispheric lateralization of affect/motivation, with the right hemisphere being specialized for negative affect and withdrawal motivation, and the left hemisphere being specialized for positive affect and approach motivation (e.g., Davidson, 2002, 2004; Davidson et al., 1990; Tomarken et al., 1992).

Unfortunately, EEG and functional imaging techniques are expensive, time consuming, limited, or impossible for use in real-world situations, and require specialized knowledge. In order to remove some of these limitations, other methods to assess these relationships have been investigated. One such method is lateralized differences in tympanic membrane temperature (TMT).

Tympanic membrane temperature may reflect hemispheric activity in frontal and temporal lobes (e.g., Schiffer et al., 1999). Increased hemispheric activity is associated with increased propensity to experience that hemisphere's affective/motivational state. For example, individuals with increased right hemisphere activity are more likely to experience negative affect and withdrawal motivation (e.g., Henriques and Davidson, 1991), while those with increased left hemisphere activity are more likely to experience positive affect and approach motivation (e.g., Davidson, 2004). TMT, by reflecting hemispheric activity, may therefore be predictive of emotional and motivational state.

Unfortunately, however, the relationship between TMT and hemispheric activity is by no means straightforward. Although discussion of the physiological mechanisms whereby TMT changes as a function of hemispheric activity is beyond the scope of this mini-review, it should be noted that there are several contending, and contradictory, hypotheses. For simplicity, physiological mechanisms can be grouped into two broad schools of thought, leading to opposite predictions of the relationship between TMT and emotion/motivation; (i) increased TMT on one versus the other side is associated with ipsilaterally *increased* hemispheric activity (e.g., Boyce et al., 2002; Gunnar and Donzella, 2004) and (ii) increased TMT on one versus the other side is associated with ipsilaterally *decreased* hemispheric activity (Boyce et al., 1996; Helton, 2010; Helton et al., 2009a). Thus, based on proposed physiological mechanisms alone it is not clear *a priori*, in any given circumstance, if, for example, *increased* left TMT is associated with positive emotion [via (i) above] or with negative emotion [via (ii) above].

Examination of the TMT-affect/motivation literature could help elucidate TMT-hemispheric activity relationships, and shed light on the physiological mechanisms that underlie them. Additionally, should a clear predictive relationship between TMT and affect/motivation exist, such a finding would be eminently useful for both research and clinical purposes. From a research perspective, lateralized differences in TMT might enable real-time monitoring of hemispheric activity in real-world conditions. From a clinical perspective, lateralized differences in TMT might serve as a corroborating marker of mental illnesses associated with specific affective dysregulation.

Thus, the purpose of this mini-review is to (i) determine if lateralized differences in TMT are systematically related to emotion/motivation and (ii) if so, by inference, is increased TMT associated with ipsilaterally *increased* or with ipsilaterally *decreased* hemispheric activity.

THE LITERATURE

A review of the literature revealed a total of 12 articles (including one in press from the authors' laboratories) meeting the following criteria: (i) use of TMT as a dependent measure, (ii) affect or approach/withdrawal behavior as either dependent or independent variables; (iii) analyses allowing determination of affect or approach/withdrawal-TMT relationships; and (iv) humans as participants. Articles were found via a search of PubMed, using various combinations of the key words (and their main root word): "tympanic," "temperature," "emotion," "mood," "lateralization," "asymmetry," and "motivation." Articles were also found via citations listed in articles found using the above methodology.

Some articles, although including TMT and affect/motivation, were eliminated because they failed to meet one of the above criteria (e.g., Schiffer et al., 1999; Parr and Hopkins, 2000; Cherbuin and Brinkman, 2004).

A summary of the results is presented in **Table 1**.

RESULTS

GENERAL

Twelve articles were produced by five laboratories. One laboratory (Helton and colleagues) produced 42% (5), while another (Propper and colleagues) produced 25% (3). An additional laboratory produced 17% (2; Boyce and colleagues). The remaining two manuscripts came from two different laboratories (Gunnar and Donzella, 2004; Jones et al., 2011). Of the 75% (9) published after or during 2010, all but one were from the laboratory of either Helton or Propper. These results suggest that investigation of TMT-emotion/motivation is in its infancy, and that while any consistent findings may be promising, they will need to be replicated and extended by other laboratories.

Thirty-three percent (4) examined children 3–9 years of age; the other 67% (8) investigated TMT in college students. It is not clear if results of young children are generalizable to adults; brain organization, including lateralization of cerebral functions, in addition to structural organization, is subject to developmental changes (e.g., Groen et al., 2012). Because so few TMT studies exist, future research will need to address whether the same processes underlying any TMT-affect/motivational relationships are the same in children and adults.

STUDIES IN CHILDREN

Three out of four (75%) studies examining children relied on parental reports of affect/motivational orientation. The fourth (Jones et al., 2011), although investigating TMT in response to stress, did not directly assess affect or motivation, but is included below because it is relevant to the issues discussed here.

The earliest study (Boyce et al., 1996) examined parental reports of behavior and emotional orientation in 8 year old children. Boyce reported that warmer left, relative to right TMT was associated with "decreased ego resilience." Further, examination of their results indicates that increased aggression, externalizing and internalizing behavioral problems, somatization, schizoid behaviors, depression, and social withdrawal were also associated with increased left TMT. Boyce et al. suggested that increased lateralized TMT was related to ipsilaterally *decreased* hemispheric activity.

Boyce et al. (2002), in an extension and replication, examined TMT-affect/motivation relationships in four cohorts of children ages 4.5–8 years old. In contrast with Boyce et al. (1996), here it was reported that warmer left, relative to right, TMT was associated with positive affect/approach motivation, and warmer right, relative to left TMT was associated with negative affect/withdrawal motivation. Thus, these results suggest the converse of those described above, with warmer left TMT reflecting increased left hemisphere activity, and increased lateralized TMT related to ipsilaterally *increased* hemispheric activity.

It is not clear why there exists a discrepancy between the two studies; both examined children approximately the same age, and both relied on parental reports of affect/motivational orientation. However, it is notable that Boyce et al. (1996) characterized "aggression" and "problem behaviors" as negative affect/withdrawal motivation. As indicated in **Table 2**, recent work indicates that "aggression" may be considered an approach motivational state. Additionally, by definition behavioral disinhibition and impulsivity such as that reflected in "externalizing and internalizing behavioral problems," somatization, and schizoid behaviors may be considered left hemisphere, approach behaviors. Though it is not clear why social withdrawal and depression would be associated with increased left TMT, most results reported by Boyce et al. (1996), when considered in this manner, are in agreement with Boyce et al., 2002, such that increased left TMT reflects increased left hemisphere activity.

Gunnar and Donzella (2004), examining parental reports of affect and motivational orientation in 3–5 year olds, reported findings consistent with Boyce et al. (2002); warmer left, relative to right, TMT was associated with positive affect, and warmer right, relative to left TMT was associated with negative affect. Specifically, higher scores on a smiling and laughing scale were associated with warmer left TMT, while higher scores on the sadness scale were associated with warmer right TMT. Interestingly, score on the fear, anger, and shyness scales were not correlated with differential left or right TMT.

Jones et al. (2011) examined TMT in 8 and 9 year old children following a psychosocial stressor. Both left and right TMT decreased following the stressor, and there were no differences between left and right TMT. Birth weight adjusted for placental weight in the children (from previously collected longitudinal data) did correlate with left TMT after stress; children who were smaller babies with bigger placentas had higher left TMT following stress, while larger babies with smaller placentas had warmer right TMT following stress. The authors interpreted their findings as indicating *increased* right hemisphere activity following stress in children with small sizes and larger placentas.

That is, findings were put into a framework wherein increased lateralized TMT is associated with *decreased* ipsilateral hemispheric activity. However, it is interesting to note that (i) no measures of stress or mood were examined and (ii) both left and right TMT decreased equally following stress. Additionally,

Table 1 | Tympanic membrane temperature and affect/motivational orientation articles.

Article	Participant age	Task or report	Main findings	Summary
Boyce et al. (2002)	4.5–8 year olds	Parental report of affect/behavior	Increased L-R TMT associated with positive emotions and socially "competent" behaviors; decreased L-R TMT associated with negative emotions and "problem" behaviors	Warmer L TMT associated with positive/approach emotions; warmer R TMT associated with negative emotions
Boyce et al. (1996)	8 year olds	Parental report of affect/behavior	Increased L-R TMT associated with increased aggression, decreased ego resilience, depression, externalizing, and internalizing behavior problems, schizoid behaviors, social withdrawal, and somatization	Warmer L TMT associated with negative/withdrawal emotions
Gunnar and Donzella (2004)	3–5 year olds	Parental report of affect/behavior	Increased L-R TMT associated with increased smiling and laugher, decreased L-R TMT associated with increased sadness	Warmer L TMT associated with positive/approach emotions; warmer R TMT associated with negative emotions
Helton (2010)	19.97 Mean age (undergraduates)	Impulsivity assessed via performance on Go-No-Go tasks	Warmer L TMT associated with increased errors of commission and faster reaction time	Warmer L TMT associated with increased impulsivity/approach motivation; Increased R TMT associated with more "cautious" behavior
Helton and Carter (2011)	20.3 Mean age (undergraduates)	TMT assessed at baseline by male or female experimenter	Lower R TMT when measured by female investigator; Similar R and L TMT when measured by male investigator	Placed in framework of "threat assessment"; interpretation not clear
Helton et al. (2009a)	Range of 18–33 years	Attention assessed via performance on local and global sustained attention tasks	Increased R TMT associated with sustained attention to global stimuli	Warmer R TMT associated with global attention; interpreted as cognitive fatigue-related decreased R hemisphere activity
Helton et al. (2009b)	20 Mean age (undergraduates)	No affect report following possible mood induction, attention assessed via performance on the sustained attention to response task	Greater increase in R TMT compared to L TMT from pre to post-task	Warmer R TMT associated with increased attentiveness
Helton and Maginnity (2012)	21 Mean age (undergraduates)	Self-report of attention/inattention	Increased R-L TMT associated with decreased inattention	Warmer R TMT associated with increased attentiveness
Jones et al. (2011)	7–10 year olds	No affect report following stress induction	Low fetal-maternal "health" at birth associated with increased L-R TMT following stress	Warmer L TMT associated with negative emotions
Propper et al. (2010)	19.66 Mean age (undergraduates)	Self-report of affect at baseline	No association between R-L TMT and any emotion; Ar-ITMT associated with increased anger/hostility	Greater absolute *difference* between L and R TMT associated with anger/hostility
Propper et al. (in press)	Undergraduates (age not reported)	Self-report of affect following mood induction	Baseline: increased R TMT associated with increased positive affect; post-manipulation: increased R TMT associated with increased negative affect; increased L TMT associated with positive affect	Greater absolute *difference* between L and R TMT associated with anger/hostility; other results not clear

(Continued)

Table 1 | Continued

Article	Participant age	Task or report	Main findings	Summary
Propper et al. (2011)	Range of 19–21 years per group (undergraduates)	Self-report of affect following sustained unilateral visual stimulation	Increased Ar-ITMT associated with increased anger/hostility, increased R-L TMT associated with increased anger	Greater absolute *difference* between L and R TMT associated with anger/hostility; warmer R TMT associated with negative emotions

Table 2 | Affective valence × motivational state.

		Motivational state	
		Approach	**Avoidance**
Affective valence	Positive	Enthusiasm Amusement Desire/pleasure	–
	Negative	Anger Frustration Aggression	Anxiety Fear Disgust

individual differences in birth weight-placental size may be associated with individual differences in any number of other areas, including structural and functional cerebral lateralization, or in overall subjective response to "stress." If so, then the results indicate a relationship such that increased lateralized TMT is associated with ipsilaterally *increased* hemispheric activity.

The TMT-affect/motivation literature in children offers some limited evidence that (i) warmer left TMT is associated with positive affect/approach motivational states and that warmer right TMT is associated with negative affect/withdrawal motivational states; and (ii) a relationship between lateralized TMT and affect/motivation such that increased lateralized TMT is associated with increased ipsilateral hemispheric activity.

STUDIES IN ADULTS

The 67% (8) studies examining TMT-affect/motivation in adults come from two laboratories, Helton and colleagues and Propper and colleagues. All were published in 2010 or later, and all examined college students.

Helton et al. (2009a), Helton and Maginnity (2012), and Helton et al. (2009b) examined adult college students, using self-reported (Helton and Maginnity, 2012) and performance measures (Helton et al., 2009a; Helton et al., 2009b) of attention. One interpretation of focused or sustained attention is that it represents a state of approach motivation (Gable and Harmon-Jones, 2008). In all three studies, warmer right TMT was associated with increased attention. Helton et al. (2009a), investigated sustained attention in a paradigm examining local and global processing. They reported increased right TMT to be associated with increased sustained attention; they interpreted their findings as indicative of right hemisphere fatigue, and of decreased right hemisphere activity. Helton et al. (2009b) reported increased right TMT following exposure to negative pictures, and additionally following performance of a sustained attention to response task, considered as a test of sustained attention. Again, results were interpreted as indicating warmer TMT being associated with *decreased* ipsilateral hemispheric activity. Finally, Helton and Maginnity (2012) reported that decreased self-reported symptoms of inattention in college students were associated with increased right TMT.

Although Helton et al. (2009a) and Helton et al. (2009b) suggest that increased right TMT is associated with decreased right hemisphere activity, alternate explanations exist. First, clear differences in attentional capacities *per se* are known to exist between the hemispheres. Specifically, the right hemisphere is known to have a much larger role in attending generally, relative to the left hemisphere (Ramachandran and Blakeslee, 1999). Additionally, the right hemisphere is known to be particularly involved in vigilance (Warm et al., 2009). Thus, when considered from a perspective other than emotion/motivation, the above results are consistent with the notion that increased TMT on one versus the other side reflects ipsilaterally *increased* hemispheric activity. Similarly, the increased right TMT following exposure to negative pictorial stimuli supports this interpretation, given the right hemisphere's known role in negative affect/withdrawal motivation, and the results reported in studies of children's TMT.

Helton (2010) examined college students, using behavioral measures of impulsivity/approach motivation in an experimental design. In a Go-No-Go task, increased errors of commission, and faster reaction times, were associated with increased left TMT. Findings were interpreted such that increased impulsivity and approach motivation were associated with increased left TMT, and that increased lateralized TMT was indicative of *increased* ipsilateral hemispheric activity.

Helton and Carter (2011) reported effects of experimenter gender on lateralized TMT, finding warmer left, relative to right TMT when participants were tested by a female investigator. They interpreted their findings as resulting from "threat appraisal," with decreased threat detected with female researchers. Although only minimally discussed, it was suggested that warmer TMT is associated with ipsilaterally *decreased* hemispheric activity; in this case then, decreased threat is associated with increased right hemisphere activity. However, it is equally plausible that the presence of a female investigator increased approach motivation (relative to a male investigator), and that therefore increased left TMT is associated with ipsilaterally *increased* hemispheric activity.

Work from the authors' laboratories (Propper et al., 2010, 2011, in press) examined self-reported affect at baseline and following experimental manipulations. Propper et al. (2010)

examining baseline TMT-affect relationships reported that greater difference between the left and right TMT was associated with increased anger. No other TMT-affect relationships attained significance.

Propper et al. (2011), manipulated hemispheric activity via sustained unilateral gaze to examine effects on TMT. Increased left TMT was associated with increased anger collapsing across all conditions, as was the absolute difference between the left and right TMT. Though interpreted as indicating an association between negative affect (anger) and increased right hemisphere activity (that is, ipsilaterally *decreased* hemispheric activity), given research indicating that anger is an approach motivational state (Harmon-Jones and Allen, 1998), the findings are at least equally likely to suggest that increased lateralized TMT is associated with increased ipsilateral hemispheric activity. Propper et al. (in press), examined TMT following mood induction. Findings again indicated that increased difference between the left and right TMT, regardless of the direction of that difference, was associated with increased anger. Additionally, tentative evidence was presented suggesting pre versus post-task differences in the relationship between TMT and affect/motivational state, such that pre-task lateralized TMT is associated with ipsilaterally *decreased* hemispheric activity, but post-task with ipsilaterally *increased* hemispheric activity. However, the pre-task findings occurred only in men, with few participants, and in only one mood (happiness/sadness) condition. In contrast, post-task associations occurred for both calm/anxious mood and for happiness/sadness, such that lateralized TMT was associated with ipsilaterally increased hemispheric activity.

SUMMARY

The present review supports the proposal that TMT holds potential for broadly indexing lateralized brain physiology during tasks demanding the processing and representation of emotional and/or motivational states, and for predicting trait-related affective/motivational orientations. The precise nature of the relationship between TMT and brain physiology, however, remains elusive. Indeed the limited extant research has sampled different participant populations and employed largely different procedures and measures, making for seemingly discrepant findings and implications. For example, methodologically, some of the studies reviewed here examined TMT as an indicator of stable, between-subjects individual differences in affective/motivational orientation (e.g.: Boyce et al., 1996; Boyce et al., 2002; Propper et al., 2010; Helton and Maginnity, 2012), while others considered TMT as indicating within-subjects variation in affective/motivational state (e.g., Helton et al., 2009a,b; Propper et al., 2011, in press). Still others examined TMT as reflecting trait differences *in response* to state manipulations involving stress (e.g., Jones et al., 2011). Interestingly, it has been proposed that within- versus between-subjects examinations may influence TMT-hemispheric relationships, with increased TMT being associated with (i) decreased ipsilateral hemispheric activity in within-subjects designs and (ii) increased ipsilateral hemispheric activity in between-subjects designs. (e.g., Cherbuin and Brinkman, 2007; Helton, 2010; Propper et al., in press). However, the literature reviewed here reveals no clear pattern for differences in lateralized TMT as a function of consideration of state versus trait variables, and we leave it to others to investigate this suggestion further empirically.

We do propose, however, that many of the discrepancies in the TMT literature can be resolved by considering how emotional states map onto motivational systems (i.e., **Table 2**), and further examining how validated methods for inducing lateralized brain activity might affect TMT.

Traditional theories attempting to define emotional experience considered emotions as modular entities (e.g., Izard, 1991; Ekman, 1992), or sought to describe their underlying dimensions of valence and arousal (Lang et al., 1992; Russell, 2003). More recent work has demonstrated utility in defining not only the modularity of basic emotions or their underlying valence and arousal, but also considering the nature of events that elicit and reinforce emotions. The events associated with particular emotions carry underlying states that motivate certain types of behavior (Frijda, 1986; Davidson, 1998). In general, these motivational states are associated with approach or avoidance motives, both considered core elements in the organization of human behavior (Carver and Harmon-Jones, 2009). Critically, approach and avoidance motivations are reliably associated with distinct neural substrates thought to reside in the left and right brain hemispheres, respectively (Davidson, 1998; Pizzagalli et al., 2005). Thus, while affective states such as anger and fear are decidedly negative in valence and high arousal, they are associated with opposing motivational systems; anger promotes approach-related motives whereas fear promotes avoidance. With these distinctions in mind, we have suggested that many seemingly discrepant results can be at least partially resolved by considering how individual emotions map onto underlying motivational states.

More difficult to reconcile, however, are mixed reports detailing the directionality of any relationships between TMT and hemispheric activity. Several studies suggest that increased TMT is associated with decreased ipsilateral hemispheric activity (e.g., Helton et al., 2009a,b; Helton and Maginnity, 2012); others suggest the opposite (Helton and Carter, 2011). Still others suggest that hemispheric differences in TMT, regardless of direction, might reliably indicate the presence of an approach-oriented emotion such as anger (Propper et al., 2010, in press). Future research might attempt to replicate this latter effect with emotional states characterized by opposing motivations, such as fear. Individual differences in lateralization of emotion may have contributed to inconsistent relationships; research might control for these individual differences by ensuring that all participants are strongly right-handed.

We propose at least three types of continuing research that might prove successful in further detailing the relationship between TMT and emotional and motivational states. First, we propose that if TMT can be used to reliably index hemispheric activity, then actively promoting neural activity in specific hemispheres, such as via sustained unilateral gaze or trans-cranial direct current stimulation (tDCS), should elicit reliable differences in TMT. Some recent work in our laboratories suggests that this might be the case (Propper et al., 2011). Low-current

brain stimulation techniques, such as tDCS might also prove useful in temporarily increasing neural activity in one or both brain hemispheres. Second, we propose functional neuroimaging techniques such as EEG should be used to assess potential relationships between TMT, affect, and process-specific frequency bands. As reviewed above, we are aware of only one such study (Schiffer et al., 1999). Third, we propose value to continuing research examining motivational states associated with particular emotions; for instance, studies examining TMT responses to viewing stimuli reliably associated with appetitive (approach-related) versus disgusting (avoidance-related) motives.

Finally, we'd like to point out that not only may emotional/motivational states be lateralized, but so too are many cognitive processes (e.g., Hellige, 2001), offering the possibility that TMT may also reflect cognition. In fact, research suggests that TMT may reflect lateralized cognitive performance in some domains. For example, performance on a visuo-spatial task demonstrated decreased TMT, while performance on a verbal task resulted in decreased left TMT (Cherbuin and Brinkman, 2004). Thus, TMT, via being indicative of hemispheric activity, may also have potential in investigations of lateralized cognitive activity.

CONCLUSION

Sampling brain activity in "real-time" using portable and non-invasive technologies holds promise for understanding neurophysiologic correlates of real-world experiences. Though very few studies have examined whether TMT might hold value toward this goal, the extant data suggest that TMT is indeed sensitive to manipulations of emotional and/or motivational states. Precisely defining these relationships will be a critical goal for continuing research in this exciting area.

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An asymmetric inhibition model of hemispheric differences in emotional processing

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Two relatively independent lines of research have addressed the role of the prefrontal cortex in emotional processing. The first examines hemispheric asymmetries in frontal function; the second focuses on prefrontal interactions between cognition and emotion. We briefly review each perspective and highlight inconsistencies between them. We go on to describe an alternative model that integrates approaches by focusing on hemispheric asymmetry in inhibitory executive control processes. The asymmetric inhibition model proposes that right-lateralized executive control inhibits processing of positive or approach-related distractors, and left-lateralized control inhibits negative or withdrawal-related distractors. These complementary processes allow us to maintain and achieve current goals in the face of emotional distraction. We conclude with a research agenda that uses the model to generate novel experiments that will advance our understanding of both hemispheric asymmetries and cognition-emotion interactions.

Keywords: frontal asymmetry, hemispheric asymmetry, emotion, executive control, attention, EEG, prefrontal cortex, inhibition

HEMISPHERIC ASYMMETRIES IN EMOTIONAL PROCESSING

Prefrontal cortex (PFC) plays a critical role in emotion, but we are just starting to understand how complex interactions within the PFC give rise to emotional experience. One productive line of research examines hemispheric differences in emotional processing, focusing primarily on electroencephalography (EEG) studies of individual differences in frontal asymmetry as indexed by alpha oscillations. Alpha power has long been assumed to be negatively correlated with cortical activity (Pfurtscheller et al., 1996; Klimesch, 1999; Coan and Allen, 2004); this has led to the convention of describing left and right frontal *activity* as inverse of left and right frontal alpha power. Commonly, frontal asymmetry is measured as a trait (usually in the resting state) and is associated with a number of clinical, personality, and emotional factors, sometimes collectively called affective style (Davidson, 1992, 1998; Wheeler et al., 1993). Relatively low left (compared to right) frontal activity is associated with withdrawal-related traits including depression and anxiety (Thibodeau et al., 2006), shy temperament (Fox et al., 1995), dispositional negative affect (Tomarken and Davidson, 1994), and poor regulation of negative emotions (Jackson et al., 2003). In contrast, relatively low right (compared to left) frontal activity is associated with approach-related traits including dispositional positive affect (Tomarken and Davidson, 1994), trait anger (Harmon-Jones and Allen, 1998), sensation-seeking (Santesso et al., 2008), and high reward sensitivity (Harmon-Jones and Allen, 1997; Pizzagalli et al., 2005).

Frontal asymmetry does not, in general, correlate with current mood state, but with vulnerability or propensity to experience a particular state. For example, relatively low left frontal activity is observed in remitted depression (Henriques and Davidson, 1990; Gotlib et al., 1998), in the infants of depressed mothers (Field and Diego, 2008), and in those with genetic or familial risk of the disorder (Bismark et al., 2010; Feng et al., 2012). It also predicts future depression in healthy individuals (Nusslock et al., 2011). The predictive strength of frontal asymmetry led Davidson (1992, 1998) to propose that it reflects a diathesis – a characteristic way of processing emotional information which, when combined with sufficient stress, leads to disorder.

Two models have tried to capture the fundamental difference between hemispheres. The valence hypothesis (Tomarken et al., 1992; Heller, 1993; Heller et al., 1998; Berntson et al., 2011) grounds emotional asymmetry in affect, and associates left frontal cortex with positive emotion and right frontal cortex with negative emotion. The alternative motivational direction hypothesis (Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997; Harmon-Jones, 2003) grounds emotional asymmetry in action, and associates left frontal areas with motivation to approach, and right frontal areas with motivation to withdraw. These models have sparked decades of research and produced a catalog of traits, behaviors, and biomarkers that are correlated with different patterns of asymmetry (for reviews, see Coan and Allen, 2004; Harmon-Jones et al., 2010; Rutherford and Lindell, 2011).

We see two limitations with both models. The first is that they are premised on the assumption that there is a fundamental frontal asymmetry that should explain all findings. Given the diverse functions of prefrontal cortex and the complex nature of emotional processing, that assumption seems unlikely to hold (see also Miller et al., 2013). It is useful here to consider a potential analogy with language asymmetries, which exist at the levels of phonology, syntax, semantics, and prosody; each subserved by separate neural systems. Although there are overarching principles of hemispheric organization for language,

the asymmetries themselves are at least partially dissociable. A second limitation is that both models are largely descriptive. Neither specifies the mechanisms that are lateralized, or explains how they give rise to either emotion or motivation. We again see precedent established in language research, where progress was made when researchers focused on hemispheric asymmetries in the component processes of language instead of global language function. In this perspective, we draw on emerging understanding of cognition-emotion interactions within prefrontal cortex to propose the asymmetric inhibition model, which focuses on asymmetries in executive control mechanisms that allow us to control our emotions so that we can meet current goals.

COGNITION-EMOTION INTERACTIONS IN PREFRONTAL CORTEX

The past decade has seen much progress in describing the complex interplay among brain networks that subserve emotion (for reviews, see Lindquist et al., 2012; Ochsner et al., 2012; Pessoa, 2013). To summarize, the generation of an emotional response begins with subcortical structures (including amygdala and ventral striatum) that are sensitive to the presence of behaviourally relevant stimuli. These structures modulate attention to the stimulus (Padmala et al., 2010; Pourtois et al., 2013), and activate a sequence of physiological responses that prepare us to approach or withdraw (Lang and Bradley, 2010). Orbito-frontal cortex (OFC) receives input from subcortical structures and sensory cortex, and computes emotional appraisal, tagging the stimulus as either punishment or reward in the context of one's current needs (Rolls, 2004; Kringelbach, 2005). Anterior insula (AI) integrates this information with afferent projections from the body, giving rise to emotional awareness or feeling (Craig, 2009; Gu et al., 2013). Ventro-medial PFC (vmPFC) is closely associated with emotional experience and evaluation of emotional relevance for the self (Ochsner et al., 2004).

Lateral regions of PFC, together with anterior cingulate cortex (ACC), have traditionally been linked to cognitive functions, but contemporary models include these as core aspects of emotional processing (Gray et al., 2002; Ochsner and Gross, 2005; Pessoa, 2008, 2013; Dolcos et al., 2011). Ventro-lateral regions (vlPFC) support response selection and inhibition, and are part of the bottom–up ventral attention network that orients attention to behaviourally-relevant (including emotional) stimuli (Corbetta and Shulman, 2002; Viviani, 2013). Dorso-lateral regions (dlPFC) are involved in processes that provide top–down cognitive control, including working memory and the executive functions of updating, shifting, and inhibition (Kane and Engle, 2002; Miyake and Friedman, 2012). They are also part of the top–down dorsal attention network that directs attention in goal-relevant ways (Corbetta and Shulman, 2002; Vossel et al., 2014). Both dlPFC and vlPFC are active during forms of emotion regulation that are cognitively mediated, including cognitive reappraisal (Ochsner et al., 2012), and attentional control over emotional distraction (Bishop et al., 2004; Hester and Garavan, 2009). Sometimes dorsal and ventral regions act reciprocally, reflecting a trade-off between the ventral emotion system and the dorsal executive system (Dolcos and McCarthy, 2006; Dolcos et al., 2011; Iordan et al., 2013). However, the regions sometimes act in concert, as during cognitive reappraisal (Ochsner et al., 2012) and attentional control (e.g., Bishop et al., 2004). The exact pattern of interaction may depend on task demands and the ways in which emotional distractors compete with goal-relevant information for executive control (Pessoa, 2013). Generally, increased activation in dlPFC is associated with decreased activation in amygdala and ventral striatum (Beauregard et al., 2001; Davidson, 2002; Bishop et al., 2004; Ochsner et al., 2012), although these regions are not directly connected (Ray and Zald, 2012). Rather, dlPFC likely achieves its regulatory effects either via connections to vlPFC (Wager et al., 2008), or indirectly through control of attentional and semantic processes (Banich, 2009; Banich et al., 2009) that alter how emotional stimuli are perceived and interpreted (Ochsner et al., 2012; Vossel et al., 2014).

Hemispheric asymmetry does not figure prominently in current theories of prefrontal function in emotion. One reason might be methodological; most data come from fMRI studies that are rarely designed to assess asymmetry. When asymmetries are reported, they are often incidental to the experimental design and based on findings of significant activation in one hemisphere but not the other. However, to determine if the hemispheres differ from each other it is necessary to directly compare activation in homologous regions (Jansen et al., 2006). Such analyzes are common in studies of language asymmetries (e.g., Jansen et al., 2006; Cai et al., 2013), but rare in studies of emotion. A second issue is that there are far more studies of negative than positive emotional processing, meaning that meta-analyzes are dominated by negative studies (e.g., Phan et al., 2002; Wager et al., 2003; Ochsner et al., 2012) and individual studies rarely include both positive and negative stimuli. Unless both valences are represented, it is impossible to determine whether any observed hemispheric differences are related to valence or to emotional processes more generally.

Even given these caveats, there is little compelling evidence for asymmetries related to the *generation* of emotional experience. Amygdala activity is asymmetric; however, the asymmetry is related to stimulus properties, with the left more active for verbal and the right for visual representations (Costafreda et al., 2008; McMenamin and Marsolek, 2013). OFC is organized along a lateral gradient, with rewards represented in medial areas and punishers in lateral areas (Kringelbach, 2005), but again with no reliable hemispheric asymmetries related to either valence or motivational direction. Studies in which emotions are induced show bilateral activation of medial PFC regardless of valence (Phan et al., 2002; Wager et al., 2003). Multivoxel pattern analysis (e.g., Kassam et al., 2013; Kragel and LaBar, 2014), shows that there are distinct patterns of activity associated with positive and negative emotional experience, but these are broadly and bilaterally distributed across ventro-medial and orbito-frontal regions. There is, however, some evidence for asymmetries in the cognitive control of emotion associated with lateral PFC (Wager et al., 2003; Ochsner et al., 2012). We return to this below.

THE ASYMMETRIC INHIBITION MODEL

The absence of consistent asymmetries in fMRI studies stands in contrast to robust findings of emotion-related asymmetries

in EEG studies. How can we reconcile these findings? We start with an important observation – that EEG asymmetries are seen in alpha power. The assumption underlying all EEG asymmetry research is that alpha is inversely correlated with cortical activity. Therefore, asymmetric alpha levels are taken to reflect greater cortical activity in the hemisphere with lower alpha (Coan and Allen, 2004). This assumption is overly simplistic and does not reflect current knowledge of either the differentiation of prefrontal networks or the functional role of alpha oscillations. Few studies of EEG asymmetry use source localisation procedures, but those that have done so localize alpha asymmetries to dlPFC (Pizzagalli et al., 2005; Koslov et al., 2011). More generally, studies that measure simultaneous EEG and resting state fMRI find alpha to be inversely correlated with activity in the dorsal fronto-parietal network that coordinates activity between dlPFC and posterior parietal cortex (Laufs et al., 2003; Mantini et al., 2007) and plays an important role in the top–down executive control of attention (Corbetta and Shulman, 2002), primarily through modulations of sensory processing (for review, see Vossel et al., 2014). Functionally, alpha oscillations play a key role in attentional control and gating of perceptual awareness (Hanslmayr et al., 2011; Mazaheri et al., 2013).

The strong association between alpha and the fronto-parietal network leads us to propose that EEG asymmetries reflect the integrity of executive control mechanisms that inhibit interference from irrelevant emotional distractors. Executive control holds goal-relevant information in working memory in order to prioritize attention to relevant (over irrelevant) information (Desimone and Duncan, 1995; Kane and Engle, 2002; Lavie, 2005). Emotional stimuli are strong competitors for processing resources – this is adaptive, because they have such high behavioral relevance. But sometimes success depends on our ability to ignore the emotional stimulus and get on with the task at hand. With the Asymmetric Inhibition Model, we propose that mechanisms in left dlPFC inhibit negative distractors, and those in right dlPFC inhibit positive distractors. As we detail below, the model both accounts for much existing data and yields specific, testable predictions about how manipulations of executive control should affect hemispheric asymmetry.

EXISTING EVIDENCE FOR THE MODEL

Our goal here is not to systematically review all research on emotional asymmetry (see comprehensive reviews by Coan and Allen, 2004; Harmon-Jones et al., 2010; Rutherford and Lindell, 2011). Rather, we provide examples to demonstrate that many existing asymmetries can be interpreted in terms of executive control. In the clinical literature, for example, trait EEG asymmetries predict vulnerability to several emotional disorders that are also characterized by difficulties with executive control. Those that are associated with relatively low left frontal activity (such as depression and anxious arousal) entail difficulty in disengaging attention from negative information (Eysenck et al., 2007; Cisler and Koster, 2010; De Raedt and Koster, 2010; Gotlib and Joormann, 2010). Poor self-regulation and addiction, both associated with relatively low right frontal activity, entail difficulty in inhibiting positive distractions (Bechara, 2005; Garavan and Hester, 2007; Goldstein and Volkow, 2011).

In experimental contexts, the model predicts that EEG asymmetries should be correlated with ability to control emotional distractions. Although most EEG studies focus on personality traits or emotional responses, a few recent studies have tested relationships between trait asymmetry and attention. In all studies, emotional faces were used as cues, but the facial expressions themselves were task-irrelevant. In a spatial cueing task, people with low left frontal activity showed difficulty disengaging from angry (but not happy) faces (Miskovic and Schmidt, 2010). In our own lab (Grimshaw et al., under review) we found similar results using a dot-probe task, which can be used to indicate the capture of attention by an emotional stimulus. Participants with low left frontal activity had difficulty shifting attention away from angry (but not happy) faces, but those with high left frontal activity were unaffected by the faces. Pérez-Edgar et al. (2013) had participants perform the same dot-probe task after an emotional stressor. Those who responded to the stress by increasing left frontal activity showed no attentional biases in the dot-probe task, but those who failed to do so showed biases to angry (but not happy) faces. All these studies are consistent with the idea that left frontal activity, as measured in EEG, reflects of the ability to recruit executive control processes that inhibit negative distractions when they are contrary to current goals.

Neuroimaging studies provide some evidence consistent with the model, if we are mindful of the caveats identified in Section "Cognition-Emotion Interactions in Prefrontal Cortex". We focus on studies in which the emotional stimulus or dimension is task-irrelevent and must be ignored (e.g., emotional Stroop, irrelevant emotional flankers). These tasks consistently produce greater activation for emotional than neutral distractors in dlPFC, and often in vlPFC. Compton et al. (2003) found increased activation in left dlPFC during presentation of negative words in an emotional Stroop task. Failure to recruit left dlPFC in the face of negative distraction has been associated with depression (Engels et al., 2010; Herrington et al., 2010), anxiety (Bishop et al., 2004), trait negative affect (Crocker et al., 2012) and schizotypy (Mohanty et al., 2005). Positive stimuli (including erotica, foods, and addiction-related cues) can also tax executive control processes (Pourtois et al., 2013). Control over positive distractions is commonly associated with activity in right vlPFC (Beauregard et al., 2001; Hester and Garavan, 2009; Meyer et al., 2011) and sometimes in right dlPFC (Beauregard et al., 2001).

Across these EEG and neuroimaging studies, there is stronger support for left lateralization in the inhibition of negative stimuli than right lateralization in the inhibition of positive stimuli, even in studies that used both positive and negative stimuli (e.g., Compton et al., 2003; Pérez-Edgar et al., 2013). This is problematic for our model, because support depends critically on the hemisphere by valence interaction. One possible explanation for this imbalance is that most studies of emotional distraction have used emotional faces or words as stimuli. Although these stimuli can be matched on *subjective* ratings of arousal, negative words and faces typically produce more behavioral interference than positive stimuli (Pratto and John, 1991; Horstmann et al., 2006), suggesting that they are more taxing for executive control systems. A better test of the model would use positive and negative stimuli such as pictures of scenes,

which have equivalent potential to attract and hold attention (e.g., Schimmack, 2005; Vogt et al., 2008). Consistent with this speculation, the studies that associate inhibition of positive distraction with right lateral PFC all use emotional pictures as stimuli.

As correlational methods, EEG and fMRI cannot establish causal relationships between neural activity and function. However, brain stimulation methods, including transcranial magnetic stimuluation (TMS) and transcranial direct current stimulation (tDCS) can directly alter neural function and so establish causality. In clinical research, activation of left dlPFC with both TMS and tDCS is effective in the treatment of depression (Kalu et al., 2012). Consistent with the asymmetric inhibition model, treatment appears not to alter mood directly, but to improve executive control so that patients are better able to control negative biases (Moser et al., 2002). Conversely, right-sided stimulation affects motivation to approach positive stimuli. For example, activation of right dlPFC leads to reductions in both craving (Boggio et al., 2008; Fregni et al., 2008) and risky decision-making (Fecteau et al., 2007).

AN AGENDA FOR FUTURE RESEARCH

We are not the first to suggest that emotional asymmetries reflect inhibitory processes (see Terzian, 1964; Jackson et al., 2003; Davidson, 2004; Coan et al., 2006, for explicit statements about asymmetries in inhibitory or regulatory functions). We extend this tradition by specifying a neurologically and cognitively plausible mechanism through which hemispheric differences in emotional processing might emerge. The asymmetric inhibition model draws on our increasingly sophisticated understanding of prefrontal function. In doing so, it not only provides explanation of many existing findings, but also suggests new experimental approaches that will move our conceptualization of emotional asymmetry beyond its current descriptive level.

The model argues for a shift in focus from the study of emotion *per se* toward the study of executive processes that are subserved by lateral PFC and the dorsal fronto-parietal network. Experiments should draw on the rich literature in cognitive psychology that has identified ways to target specific components of executive control. A simple but useful paradigm involves use of irrelevant distractors (e.g., Forster and Lavie, 2008). The "goal" is an emotionally neutral task, such as finding a target letter in a display that is flanked by irrelevant distractor images, which can be either emotional or neutral. One can then manipulate the availability of executive control in order to assess its role in inhibition. For example, increasing working memory load decreases the availability of executive control and its ability to inhibit irrelevant distractors (Lavie et al., 2004; Hester and Garavan, 2005; Carmel et al., 2012). Conversely, motivational manipulations enhance relevance of the goal and increase ability to inhibit distractors (Pessoa, 2009; Hu et al., 2013). These paradigms can be used in combination with fMRI and EEG recordings to determine whether positive and negative distractions are controlled by dissociable mechanisms, and whether those are differentially lateralized.

Because of inherent limitations in EEG and fMRI approaches, stimulation studies using TMS and tDCS are important for establishing causal relationships between prefrontal function and emotional inhibition. Brain stimulation may be particularly useful in hemispheric asymmetry studies, because it provides access to higher order frontal processes that are not as amenable to experimental manipulations (such as lateralized perceptual input) that have been used to study asymmetries in other domains. The asymmetric inhibition model makes specific predictions about the effects of lateralized stimulation on inhibition. Activation of left dlPFC should improve ability to inhibit negative (but not positive) distractions; activation of right dlPFC should improve ability to inhibit positive (but not negative) distractions.

The asymmetric inhibition model differs from other accounts of emotional asymmetry in two ways. First, it does not associate an entire hemisphere with a specific emotional or motivational state; rather it focuses on one asymmetry in a single mechanism, allowing it to generate specific and testable predictions. Second, the model turns conventional wisdom on its head; associating left PFC with the inhibition of withdrawal (instead of the support of approach), and right PFC with the inhibition of approach (instead of the support of withdrawal). The model is therefore consistent with current work on cognition-emotion interactions that emphasizes the role of lateral PFC in inhibitory executive control. Although we have shown here the value of incorporating cognition-emotion interactions into models of hemispheric asymmetry, we also think that models of cognition-emotion interaction would benefit from more careful consideration of hemispheric differences. Integration of perspectives should yield richer understanding of emotional processes.

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