MANUAL SKILLS, HANDEDNESS, AND THE ORGANIZATION OF LANGUAGE IN THE BRAIN

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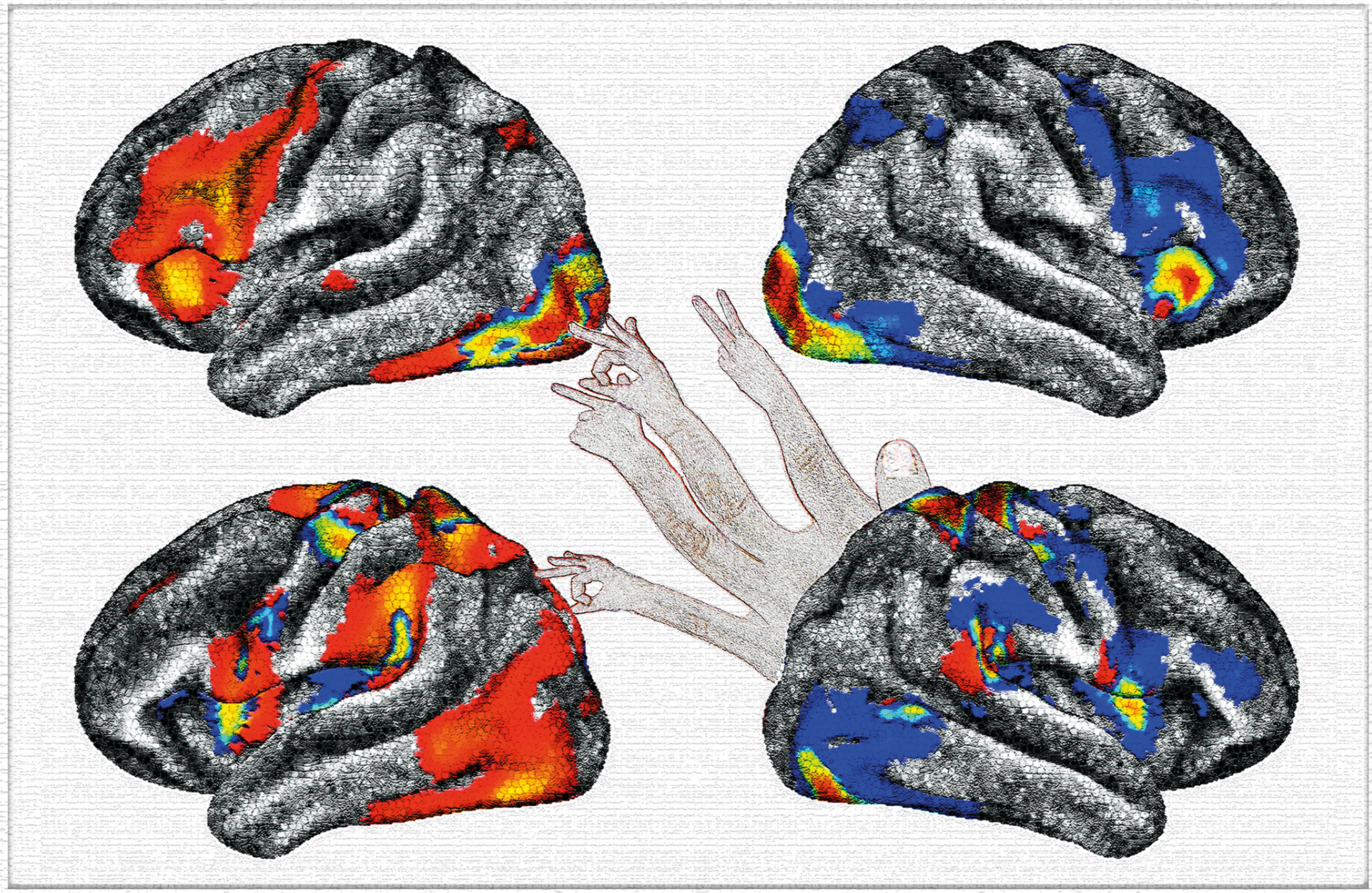

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MANUAL SKILLS, HANDEDNESS, AND THE ORGANIZATION OF LANGUAGE IN THE BRAIN

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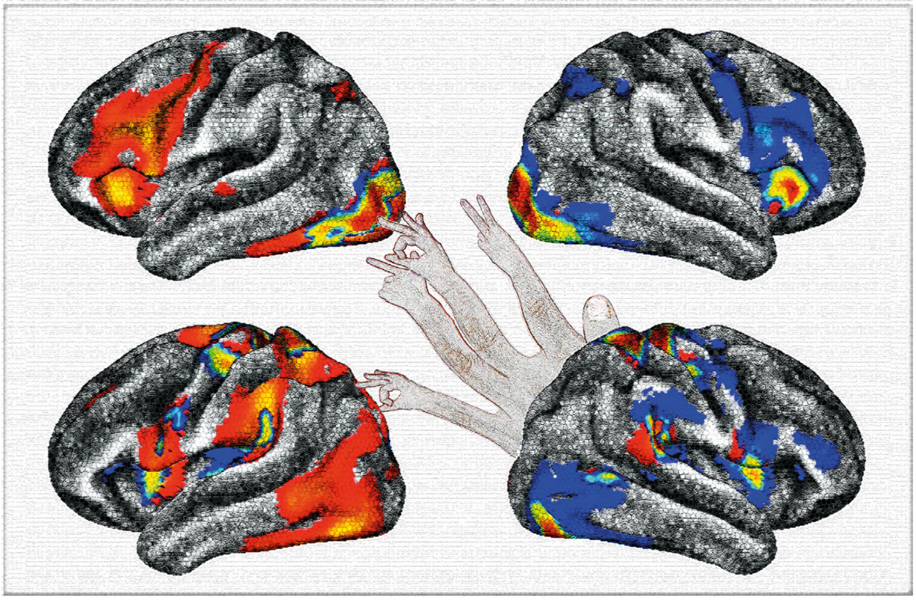

Artistic renderings of neural activity underlying language (top) and praxis (bottom) in their typical (left) and atypical (right) forms, their overlap ("cold" to "hot" colors), and the linking of manual praxis and language via gestures. Created by Gregory Króliczak by adapting outcomes from his Maestro 2011/02/A/HS6/00174 research grant, and an idea from a photo in "Why Are So Few People Left-Handed?" by Alasdair Wilkins.

Whereas the cerebral specialization for skilled manual actions (praxis) seems closely linked to dominance for language, with both functions left lateralized in the vast majority of humans, the neural correlates of hand preference are still less well understood. Indeed, as a combination of inherited and non-inherited genomic factors (i.e., direct parental and concealed environmental contributions), handedness – in contrast to language – is less likely to have strong genetic indices and clearly lateralized functional organization. What about eye dominance, unimanual and bimanual object manipulation, and gestures, or attentional systems and the related egocentric or allocentric coding of space? Are these different categories functionally and structurally interconnected? Is their development and contribution to task performance linked, even if they are differently lateralized? How are they connected to language learning or its development?

In trying to understand these relationships and their neural underpinnings we obtain a new insight into fundamental human behaviors, which depend either on shared or distinct cerebral resources that must, nevertheless, be harmonized by higher-order cerebral processing. In this Research Topic we assembled a dozen of original research contributions, as well as articles with more theoretically-driven perspectives, that directly speak to these issues. Hopefully this work will serve as a foundation for further discussions and will stimulate new research in this fascinating domain.

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EDITORIAL
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Editorial: Manual Skills, Handedness, and the Organization of Language in the Brain

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Keywords: hand preference, cerebral dominance, brain functioning, sensorimotor control, higher-order processing, skilled actions, praxis

Editorial on the Research Topic

Manual Skills, Handedness, and the Organization of Language in the Brain

Hand preference and cerebral dominance for some aspects of language processing are hallmarks of human brain functioning. Yet, their mutual relationships, similar to interrelations between hemispheric dominance for low-level sensorimotor control of the hand and the representations of higher-order, skilled actions (praxis) still remain unclear. Whereas in some accounts (Liepmann, 1900, 1908; Geschwind and Galaburda, 1985; Heilman, 1997; see also Goldenberg, 2013b) right handedness reflects (at least in part) the functioning of the left-lateralized manual praxis system, evidence from majority of left-handers weakens such a notion because they often represent praxis skills in their motor non-dominant—left—hemispheres, too (Lausberg et al., 1999; Frey et al., 2005; Goldenberg, 2013a; see also Gonzalez and Goodale, 2009; Grabowska et al., 2012; Haberling and Corballis, 2015; Kroliczak et al., 2016; cf. Carey et al., 2015). Although the putative links between praxis and language, and their interactions with handedness, have been long considered (Dejerine and Andre-Thomas, 1912; Heilman et al., 1973, 1974; McManus, 1985; Annett and Alexander, 1996; Meador et al., 1999), more recent studies clarify their relationships (Króliczak et al., 2011; Vingerhoets et al., 2013; Biduła and Króliczak, 2015; Goldenberg and Randerath, 2015; cf. Goldenberg, 2013b), further strengthening the idea that they are contingent on each other (Vingerhoets, 2014; Króliczak et al., 2018). Moreover, evidence from individuals with rarer forms of brain dominance now supports the idea that there is a longstanding evolutionary origin to the cerebral arrangement and distribution of both related and complementary skills, e.g., praxis and language vs. attention (Grabowska et al., 1994; Corballis, 2003; Cai et al., 2013; Goldenberg, 2013b).

The primary goal of this Research Topic is to present new pieces of evidence on the neural and functional organization of language and praxis, their links (or lack of thereof) with handedness and low-level motor skills, as well as behavioral consequences of their representations for other functions. Among the 12 contributing Original Research Articles, the considered functions include short-term tactile learning of Braille reading, visual word and number processing, and visuospatial discrimination. Yet, because the neural underpinnings of these functions are often strongly lateralized in the human brain, and may have common ancestry, their evolution and development is discussed in two Hypothesis and Theory articles.

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EVOLUTION AND EARLY DEVELOPMENT OF CEREBRAL AND BEHAVIORAL ASYMMETRIES

The evolution of language and tool manufacture is considered by Corballis in the context of behavioral asymmetries that emerged in humans. Evidence is discussed that such asymmetries must have developed in an independent manner, triggered by multigenetic sources, rather than a single overriding principle. It is also emphasized that representations of language and tool-use skills are rather poorly correlated with handedness. The relation of the individual development of hand preference to the critical development of human basic sensorimotor and cognitive abilities is, nevertheless, assumed in Michel. Based on earlier ideas that hand preference acquisition precedes unimanual object manipulation, and that both these skills must precede role-differentiated bimanual manipulation of objects, this contribution provides a description of an ideal paradigm for testing their development and relationships. The importance of studying developmental differences of cognitive skills across handedness is also emphasized.

LANGUAGE LATERALITY, ITS SOURCES, AND (IN)ACTIVITY-DEPENDENT WORD PROCESSING AND LEARNING

Unique characteristics of atypical organization of language are considered by Biduła et al. Whereas, most of atypical cases are indeed found in left-handers, they are also present in ambidextrous and right-handed people (cf. Carey and Johnstone, 2014). Indeed, Biduła et al. demonstrated that although group results indicate mirror-reversed organization of language in atypical participants, evidence for this is less compelling at an individual level of analysis. The relationships between language laterality and handedness are also discussed by Schmitz et al., but now from the point of genetic influences. Evidence is shown that handedness and language organization are complex phenotypes that are ontogenetically independent. This report ends with conclusions that genes involved in ontogenesis of handedness contribute primarily to structural development, whereas genes underlying language laterality also contribute to the development of other cognitive processes (but seem also associated with mental and neurological disorders).

Given language-praxis links, certain kinds of actions, or inaction, could affect language processing and learning. For example, changes in motor system functioning could flexibly influence comprehension and acquisition of words (cf. Shebani and Pülvermuller, 2018). An intriguing paper by Yasuda et al. demonstrates that while peripheral body states influence action verb processing, in contrast to a strong embodiment view, constrained arm posture affected responses to both manual and non-manual action verbs. The opposite issue, that is, an impact of word processing on movement kinematics was investigated by Rugani et al. They showed that automatic numerical processing affects action execution in a context of kicking small balls with the index finger. Their participants responded faster to small numbers while kicking the ball to the left, and vice versa. Notably, Rugani et al. argue that similar paradigms could be used to study the impact of cognition on action in an unbiased way.

Learning new vocabulary can be a challenge, especially in elder people. Yet, as Heim and collaborators show (Heim et al.), a nap, in contrast to activity or even rest, helps to consolidate language learning. While these results are less relevant to the language-praxis debate, their translation to clinical settings for improvement of speech-language therapy following brain injuries would be welcome. Still, in some circumstances learning to read new words is not possible without the involvement of certain kinds of actions, as in tactile learning of Braille (Debowska et al.). This study established that even short-term tactile training can introduce functional and structural changes in the fusiform gyrus, linked to visual processing of language, including single word reading. This is yet another demonstration how language and praxis can be related.

WHEN HANDEDNESS DOES NOT MATTER, DOES IT?

Some manual actions seem so simple that one would expect mainly contralateral control of their performance. Yet, as Begliomini et al. show, grasping with the left (dominant) hand in left handers is not controlled only by the right (contralateral) hemisphere. They found increased connectivity with the left hemisphere parieto-frontal resources. Notably, the right (non-dominant) hand is controlled as in right-handers. These outcomes are consistent with a notion that hemispheric specialization for higher-order visuomotor control does not depend on handedness (Gonzalez et al., 2006). Nevertheless, reports on the impact of handedness, the used hand/eye, and/or other cognitive abilities on performance of the line bisection task (Ochando and Zago), and left-right discrimination (Constant and Mellet) reveal a more complex picture. In the line bisection task, performance depends on integration of differently weighted visuospatial hemispheric mechanisms, the motor component of the used hand, and individual laterality factors. When they are congruent, the strongest behavioral biases are observed. As to left-right discrimination, left-handers were found better at identifying their left hands and verifying "left" propositions. Nonetheless, numerous interactions of other factors provide new insights into the links between cognitive skills and left-right discrimination.

FUNCTIONS STILL TO-BE-TESTED IN LEFT-HANDERS

The last three papers focus entirely on specific aspects of motor control. They shed new light on the impact of spatial alignment and response hand in processing visual illusions (Scocchia et al.), competition between functional and situational affordances (Roche and Chainay), and the influence of action mode on efficiency in rule- vs. plan-based movements (Scheib et al.). Of course, the studied skills are less likely to depend on linguistic representations. Yet, although some differences contingent on the responding hand were suggested, they are less likely to emerge when directed at tools. As such, these approaches can stimulate new research and reveal new findings of theoretical interest for our debate.

CONCLUSIONS

This Research Topic highlights the findings on the relationships between manual skills and language, and their putative links to handedness and associated motor functions. Research showing both similarities and disparities in their organization in right-handed and left-handed (but also ambidextrous) individuals is featured. The debate includes the evolution and early development of cerebral and behavioral asymmetries, as well as their genetic foundations. We hope that further discussions and research ideas will emerge out of this work.

AUTHOR CONTRIBUTIONS

GK conceived this work and drafted the editorial. CG and DC contributed intellectually to this work, revised, and approved the draft for publication.

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The Evolution of Lateralized Brain Circuits

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In the vast clade of animals known as the bilateria, cerebral and behavioral asymmetries emerge against the backdrop of bilateral symmetry, with a functional trade-off between the two. Asymmetries can lead to more efficient processing and packaging of internal structures, but at the expense of efficient adaptation to a natural world without systematic left-right bias. Asymmetries may arise through the fissioning of ancestral structures that are largely symmetrical, creating new circuits. In humans these may include asymmetrical adaptations to language and manufacture, and as one or other hemisphere gains dominance for functions that were previously represented bilaterally. This is best illustrated in the evolution of such functions as language and tool manufacture in humans, which may derive from the mirror-neuron system in primates, but similar principles probably apply to the many other asymmetries now evident in a wide range of animals. Asymmetries arise in largely independent manner with multi-genetic sources, rather than as a single over-riding principle.

Keywords: brain asymmetry, evolution, handedness, gesture recognition, mirror neuron system

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INTRODUCTION

Part of the reason for the fascination with handedness and cerebral asymmetry is that they seem to arise from a system that is for the most part structurally symmetrical, suggesting the operation of some non-material force—and perhaps even encouraging a Cartesian notion of mind over matter (Corballis, 1980). Nevertheless lateral asymmetries can scarcely be understood or even defined except in relation to symmetry. Humans belong to the vast clade of animals known as the *bilateria,* going back some 550 million years, and characterized by near symmetry about the midsagittal plane. This bilateral symmetry makes us almost indistinguishable from our reflection in the mirror, and may be an adaptation to the fact that for freely moving animals, the natural world is essentially indifferent with respect to left and right. So it is that we have limbs and sense organs arranged in bilateral pairs, and even the brain is more obviously symmetrical than it is asymmetrical. You would be hard-pressed to decide whether a picture of the brain is normal or mirror-reversed, although there are a few small give-away signs.

It is against this fundamentally symmetrical plan that asymmetries sometimes arise, and are of interest. Structural asymmetries are especially evident in the way internal organs are located, with the heart, stomach, and spleen displaced to the left, the liver and gall bladder to the right. Some asymmetries, such as the asymmetrical gallop of a horse, or human preference for one or other hand, are more apparent from function than from structure. This also seems to be true of the human brain, which functions in well-documented asymmetrical ways that are all the more remarkable given its apparent anatomical symmetry.

The pressure toward asymmetry may have to do, at least in part, with packaging and efficiency, especially in internal structures that are largely independent of external constraints. It would simply be inefficient to pack a suitcase while retaining perfect symmetry of its contents; rather, you fit the contents in to make optimal use of the space. Similarly, an automobile retains external symmetry for efficient movement and maneuverability, while its internal parts are asymmetrically organized. Sheer efficiency may therefore have guided the placement of internal bodily organs such as the stomach, which processes food regardless of the manner of its arrival—or its departure. The heart, too, functions internally and is asymmetrical, but retains a degree of symmetry because it must pump blood to both sides of the body.

There is greater pressure for the retention of symmetry in the brain than in the internal organs of the body, because it is involved in coordination of symmetrical actions such as walking or swimming, and the processing of input from symmetrical sense organs. As the brain increases in size and complexity, though, there would be increased demand for asymmetrical packaging, and this pressure would be enhanced by constraints on the size of the skull. This is especially true of bipedal animals, since the demands of upright walking constrains the size of the birth canal, which in turn restricts the size of the head. These constraints conflict with heightened demands for cognitive processing, especially in animals such as humans where survival depends on complex social interactions and the manufacture of tools and habitable environments. In humans, these competing pressures create what has been termed the "obstetrical dilemma," a hypothesis to explain why childbirth is so difficult, and leads to dangerously early birth normally requiring assistance (Washburn, 1960)—yet we need large brains to cope with the complexities of our lives on the planet. The pressure for larger brains in a constrained skull can also explain why the human brain is exceptionally wrinkled and folded, like an old automobile crushed for infill. The same conflict might also explain why asymmetry seems especially pronounced in the human brain, since reducing redundancy and duplication makes better use of the restricted brain space.

THE EVOLUTIONARY TRADE-OFF

The trade-off between symmetry and asymmetry is well illustrated, at least in humans, by the hands, and was perhaps a consequence of bipedalism, which freed the hands from involvement in locomotion. The programming of complex actions is most efficiently achieved by an asymmetrical system in the brain rather than one duplicated between hemispheres, yet equal division between the hands is adaptive in simple spatial activities like reaching or plucking, and even in locomotory activities such as swimming. An interesting example is provided by Watson and Kimura (1989), who found that the two hands were equally adept at blocking fast-moving missiles (table-tennis balls), but one hand was much more adept at throwing them than the other. Athletes involved in sports like cricket generally catch well with either hand but throw almost exclusively with just one hand. Activities involving cooperation between the hands, like unscrewing a lid or hammering a nail, also lead to different specializations. As a fairly general rule one hand, usually the left, is used for holding and the other for operating (Bruner, 1968).

Other bipedal species similarly prefer one or other hand in manipulation or in bringing food to the mouth. These include some species of kangaroo (Giljov et al., 2015), which are predominantly left-handed in feeding, and some species of parrot also preferentially use the left foot when picking up bits of food while perching on the right foot (Rogers, 1980; Friedman and Davis, 1938). Some 65–70 percent great apes favor the right hand in various tasks (e.g., Hopkins et al., 2011), with the possible exception of orangutans (Rogers and Kaplan, 1996), but the incidence is lower than that in humans, which stands at around 90 percent. Cerebral asymmetry itself is pervasive in the animal kingdom (Rogers et al., 2013). A general left-hemispheric bias for action dynamics exists in many species, including marine animals and some primates (MacNeilage, 2013). Conversely, a right-hemisphere dominance for emotion seems to be present in all primates so far investigated, suggesting an evolutionary continuity going back at least 30 to 40 million years (Lindell, 2013).

The sense of a trade-off is also suggested by the fact that cerebral and behavioral asymmetries are seldom if ever universal, unlike asymmetries of the internal organs in which the vast majority of individuals show the same asymmetries. Where a given direction of asymmetry is the norm, the proportion of individuals exhibiting the asymmetry lies within the range of about 65–90 percent—a range that seems to apply across the animal kingdom (Ghirlanda and Vallortigara, 2004), with human handedness and cerebral asymmetry at the top of the range. In contrast, the asymmetries of the internal organs are remarkably consistent, with only about one in 10,000 people showing reversal, a condition known as situs inversus (Torgersen, 1950). In the brain, the relative demands of symmetry and asymmetry may therefore be labile, and there may even be population-level advantages in variation. Perhaps the inclusion of a minority of left-handers led to an advantage in warfare or in some sports, but only so long as they remained a minority. There is some evidence that mixed handers are more creative than right- or left-handers handers (Shobe et al., 2009), suggesting that in some endeavors bilaterality may outweigh asymmetry.

Cerebral asymmetry for language is often linked to handedness. For example, Bruner (1968) suggested that the functional difference between the hands could be extrapolated to the cerebral hemispheres, with the right hemisphere holding the context while the left provides the operation, the actual output. More generally, the link between handedness and brain asymmetry may have come about in the evolution of complex manual activities such as the manufacture and use of tools, or more directly through gestural communication itself. Indeed there are some compelling reasons to suppose that language evolved from manual gestures rather than from primate calls (e.g., Hewes, 1973; Corballis, 2002). For example, it has proven virtually impossible to teach great apes anything resembling vocal language, but gestural forms of communication with language-like properties seems to come about quite naturally in chimpanzees, bonobos, and gorillas (Savage-Rumbaugh et al., 1998; Patterson and Gordon, 2001), and is evident in the activities of chimpanzees in the wild (Hobaiter and Byrne, 2011). Again, signed languages are purely gestural, with no functional acoustic component, yet carry all the hallmarks of true language (Emmorey, 2002).

MULTIPLE CIRCUITS, MULTIPLE GENES

Nevertheless handedness itself is actually rather poorly correlated with cerebral asymmetry for language. Some 95–99 percent of right-handers are left-hemispheric for language, but so are some 70–80 percent of left-handers (Corballis et al., 2012). Different aspects of hemispheric asymmetry are also poorly correlated; one study, for example, shows zero correlation between left-hemispheric dominance for language and right-hemispheric dominance for spatial attention (Badzakova-Trajkov et al., 2010). In another study of brain activity recorded in participants at rest, factor analysis of asymmetries at different sites indicated four independent lateralized networks, two favoring the left hemisphere and two the right (Liu et al., 2009). Such findings suggest that cerebral asymmetry is not due to some all-encompassing gradient, but depends on multiple influences. Indeed, attempts to locate a single laterality gene have largely failed, and it has been suggested that as many as 40 different genes may be involved (McManus et al., 2009).

Factor analyses of task-evoked brain activity also suggest independent circuits. In one study fMRI responses to word generation, processing of faces making emotional expressions, and the landmark test (a measure of spatial attention) yielded three orthogonal factors (Badzakova-Trajkov et al., 2016). One was linked to the language task and represented a left-hemispheric circuit including the pars opercularis and the pars triangularis (together comprising Broca's area), and the inferior and superior parietal lobules. Another was linked to spatial attention, with right-hemispheric activation predominantly in the pars opercularis, the inferior and superior parietal lobules, and the supramarginal gyrus. The third was also a right-hemispheric circuit linked to face processing, with activation predominantly in the pars triangularis, the fusiform gyrus, and the middle temporal gyrus.

Independent circuits also seem to exist within the left hemisphere. Gonzalez et al. (2006) found that left-hemispheric specialization for the visual control of action was unrelated to handedness, while Króliczak and Frey (2009) identified a circuit concerned with the planning of pantomimes and intransitive gestures, also shown to be independent of handedness (Króliczak et al., 2016). There may be a closer relation, though, between pantomime and language. Vingerhoets et al. (2013) compared samples of those with typical and atypical language dominance, and found strong correlations between brain asymmetry for word generation and for pantomiming tool use. Eighty percent of the participants in each group were left-handed, leaving some question as to whether the relation would hold among right-handers. In a sample of right-handers, Xu et al. (2009) found that spoken language and observation of symbolic gestures, some of which included pantomimes of simple tool use, activated a common left-lateralized network.

Again, though, factor analysis opens the possibility of a more comprehensive account. In one study, both right- and left-handed participants performed simple acts of language production and comprehension, along with observations of action, and factor analysis of laterality measures produced three orthogonal factors, suggesting the existence of three independent networks (Häberling et al., 2016). One was clearly language related, loading on activity in language areas when the participants undertook either of the language tasks. Another, loading on parietal and frontal areas, was activated by observation of actions and was strongly associated with handedness. The third involved frontal and temporal areas partly overlapping with the language circuit, although uncorrelated with it. This circuit was also associated with action observation, but was independent of the handedness circuit. It was the least lateralized and may well be the residue of the original mirror system, dedicated to simple acts such as grasping and reaching (Marangon et al., 2015), but perhaps elaborated to include hand-independent aspects of pantomime (Króliczak and Frey, 2009).

HOW LATERALIZED CIRCUITS EVOLVE

It is unlikely that new circuits in the brain emerge *de novo*, but are formed from ancestral systems. This can occur in several ways: through expansion and fissioning of an ancestral system into separate systems, through copying and differential modification of an existing circuits, or sometimes through modified circuits fusing to create new functions. These processes in turn can involve the splitting of genes, rather than the emergence of new genes (Oakley and Rivera, 2008). The evolution of new and more specialized circuits may also have increased pressure to lateralization, enabling more efficient packaging and less redundancy and competition. Such pressure may have been especially intense in hominin evolution, as our forebears adapted to increased social and environmental complexity.

In this last example given above, the three circuits may well have derived from the primate mirror system, which responds both when a monkey makes an intentional movement such as grasping a piece of food, and when it observes another individual making the same movement (Rizzolatti and Sinigaglia, 2010). This ancestral system seems to provide an ideal platform for the evolution of language, since it relates the perception of action to its production, and indeed can be taken as further support for the idea that language evolved from manual gestures (Rizzolatti and Arbib, 1998; Corballis, 2002). The mirror property also provides the basis for mutual understanding between speaker and listener (or signer and watcher), an understanding that goes beyond the words themselves and is indeed necessary for effective communication (Sperber and Wilson, 2002). In that respect, language has been characterized as "underdetermined" (Scott-Phillips, 2015).

Within the left hemisphere, then, the language circuit may have fissioned from the ancestral mirror system, and may have been the first new circuit to form, since it was the most lateralized of the three. The circuit linked to handedness may have split off as an adaptation to the use and manufacture of tools, in which handedness is most strongly expressed. And as suggested above, the third and least lateralized circuit, which was independent of handedness, may be the residue of the ancestral mirror system.

A similar fissioning may explain the lateralized representation of reading. Behrmann and Plaut (2015) document evidence that the fusiform gyrus in the primate brain is specialized for face recognition. In humans, the emergence of literacy resulted in a split into a right-hemispheric system for face recognition and a left-hemispheric one for the recognition of printed words, at least among people who have learned to read (literacy is still not universal). This would also have created the asymmetry required for mirror-image discrimination, as in the distinct recognition of letters like *b* and *d* or words like *was* and *saw*. Dehaene and Cohen (2011) describe this process as the "recycling" of cortical territory, originally designated for object and face recognition, for the recognition of spoken words—and Dehaene et al. (2010) suggest that face recognition may suffer as a consequence. It is perhaps not so much a question of recycling, though, as one of the invasion of cortical territory initially dedicated to one function by a related but more specialized function.

This complementarity probably goes beyond the fusiform area. In the analysis by Badzakova-Trajkov et al. (2016), activity of Broca's area on the left in response to word generation was strongly correlated with activity on its right homolog on the right in response to the processing of videos of facial expressions. This complementarity was partitioned within Broca's area, with activation on the left stronger in the pars opercularis and that on the right stronger in the pars triangularis. Some asymmetries, then, probably arise as a secondary consequence of an asymmetry emerging in one hemisphere, so the other hemisphere assumes dominance over a function that was previously bilateral.

CONCLUSION

Although this scenario suggests that complementarity can arise in the emergence of asymmetries, it does not support the global view of the so-called dual brain, in which each cerebral hemisphere is assumed to represent complementary but global aspects of human cognition, variously characterized as linear, analytical and rational on the left, and divergent, holistic and intuitive on the right (e.g., Ornstein, 1972). This view has persisted to a remarkable degree in modern scholarship (e.g., McGilchrist, 2009) as well as in folklore, and concepts of "left-brain" and "right-brain" thinking are even listed in modern dictionaries. The American Heritage® Dictionary of the English Language (2013), for example, offers the following definitions:

> **Left-brained** *adj*: (1) Having the left brain dominant. (2) Of or relating to the thought processes, such as logic and calculation, generally associated with the left brain. (3) Of or relating to a person whose behavior is dominated by logic, analytical thinking and verbal communication, rather than emotion and creativity.
>
> **Right-brained** *adj***:** (1) Having the right brain dominant. (2) Of or relating to the thought processes involved in creativity and imagination, generally associated with the right brain. (3) Of or relating to a person whose behavior is dominated by emotion, creativity, intuition, non-verbal communication and global reasoning rather than logic and analysis.

It has become clear that cerebral asymmetries are more complex and multidimensional, both in terms of their circuitry and their genetic underpinnings. Moreover, cerebral asymmetries are never absolute; even in a strongly left-lateralized function such as language, the right hemisphere makes a significant contribution (e.g., Tailby et al., 2017), and in some individuals representation is bilateral or even predominantly right-hemispheric (Corballis et al., 2012). This suggests a more exacting approach to cerebral asymmetries, and one that takes into account its likely evolutionary precursors.

FUTURE DIRECTIONS

Much of the argument of this article is based on the discovery and analysis of lateralized circuits in the human brain, so that conclusions as to their evolution is largely speculative, or loosely based on reverse engineering to animal behavior and physiology. To gain a better appreciation of the evolutionary sequence, future research should be directed more closely to our more recent non-human forebears. Our closest living non-human relatives are chimpanzees and bonobos, with common ancestry among the three species going back some six million years. Over that period, there may have been as many as 20 distinct species of hominin (Wood, 2002), and with the exception of our own fortunate species all are extinct, so we only have fossil evidence as to any evolutionary sequence. *Homo sapiens* is thought to have emerged as a separate species some 200,000 years ago, which is about one thirtieth of the interval from the common ancestry with the great apes, and there is still uncertainty as to whether the transition was punctuational or gradual (Stringer, 2016). According to some, such as Chomsky (2010), language emerged *de novo* uniquely in humans within the past 100,000 years, well after our species emerged—a view that denies evolutionary precursors.

This view, though, is increasingly disputed (Corballis, 2017). We share a common ancestry with the Neanderthals going back some 500,000 years, with a degree of interbreeding, leading some to propose that these large-brained ancestors were cognitively very similar to our own species and probably possessed language (e.g., Dediu and Levinson, 2013; Johansson, 2013). Evidence from their tools also strongly indicates that the majority were right-handed (Uomini, 2011). Further studies of Neanderthals and the closely related Denisovans, especially now that their DNA has been extracted, may eventually bear on how cerebral asymmetry, and indeed language itself, evolved. Morgan et al. (2015) take us back even further, arguing from the manner in which people can be taught Oldowan tool-making technology that language and tool-making must have co-evolved over the past 2.5 million years.

As noted earlier, some great apes, including chimpanzees, show species-level preference for the right hand, albeit less marked, though, than in humans, and there are now techniques for adapting structural MRI for use with chimpanzees. In one recent study, Hopkins et al. (2017) report that skill in a tool-using task designed to simulate termite fishing is associated with increased leftward lateralization of the homolog of Broca's area and of the hand area of the precentral gyrus. This suggests that the relations between handedness, tool use, and language itself as documented in this article may have evolutionary roots even earlier than the separation of the hominins from the line leading to modern great apes. Another recent study reveals that even capuchins make and use stone tools (Wasserman and Thompson, 2017).

Lateralized circuits seem to characterize such distinctively human attributes as language, the use and manufacture of tools, and social engagement, and further attention to their origins in our hominin and primate forebears will be needed to fully test the account give in this article.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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How Might the Relation of the Development of Hand Preferences to the Development of Cognitive Functions be Examined During Infancy: A Sketch?

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Investigations of the relation of the development of hand preferences to the development of other sensorimotor and cognitive abilities are plagued by confusing and contradictory results. In part, the confusion derives from the failure to create accurate, appropriate, and reliable descriptions of the development of hand preferences and the cognitive or sensorimotor ability of interest. This paper sketches an ideal longitudinal study (from birth through 5 years) with a large sample size that should provide reliable evidence for the understanding of the relation of hand preferences to cognitive development. Since hand preference differences would affect the way infants engage in manual actions with objects and these differences would likely affect how they come to comprehend object relations, differences in the development of cognition across handedness groups would be a good test of certain forms of embodiment theory.

Keywords: hand preference, infants, embodied cognition, cognitive development

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INTRODUCTION

For more than four decades, I have been investigating the development of hand-use preferences during infancy. That work has identified a potential origin for the hand preference in the newborn postural asymmetry (which, in turn, may reflect intrauterine postural asymmetries) that creates a head orientation preference (HOP, Michel, 1981). The overwhelming majority of infants (68%) exhibit a reliable HOP to keep their head oriented toward their right side when supine (or seated at a 45° angle); whereas, a minority (12–14%) exhibit a reliable HOP to keep their head to their left side. The remaining 18–20% exhibit no reliable HOP.

The left or right direction of neonatal HOP predicted initial hand-use preference for contact with, and the obtaining of objects (Michel and Harkins, 1986). We proposed that this prediction was the result of the influence of HOP on arm and hand movements and the visual, tactile, kinesthetic, and proprioceptive (and perhaps even CNS corollary discharges) feedback such laterally asymmetric movements created. Such sensory feedback likely established sensorimotor circuits in the nervous system that ensured more precise sensory control of the movements of the "face-side" arm and hand resulting in an advantage for the face-side hand for object acquisition and manipulation. Moreover, we proposed that such circuits could be used as the foundation for the establishment of other sensorimotor neural circuits that would contribute to the embodiment of cognitive functions (Michel et al., 2013a, 2016).

To assess infant handedness from 5 to 14 months, my colleagues and I created an assessment procedure that was both reliable and validated on a block play session (Michel et al., 1985). In this assessment, we identified three types of manual skills when manipulating toys/objects for which hand-use preferences could be identified. These three skills were the acquisition of objects, the unimanual manipulation of objects, and the role-differentiated bimanual manipulation (RDBM) of objects. Moreover, acquisition hand preferences seemed to precede unimanual manipulation preferences and both preceded RDBM preferences during development. Indeed, we proposed that an apparent decline in the acquisition preference after 12 months was likely the consequence of acquisition skills being employed in the service of RDBM skills. That is, as the sensorimotor circuits for acquiring objects became more efficient, they could be "attached" to (or associated with) circuits for RDBM. Thus, the non-preferred hand could be employed to obtain the object so that the preferred hand could immediately initiate RDBM without the need to transfer the object into the non-preferred hand. Subsequent research demonstrated that the hand preference for acquisition predicted the later developing hand preference for unimanual manipulation (Campbell et al., 2015a) and the even later developing hand preference for RDBM (Nelson et al., 2013a; Babik and Michel, 2016).

Therefore, I proposed a cascade hypothesis for the development of hand preferences during infancy (Michel et al., 2013b). Initially, a head orientation preference facilitates the development of a preferred hand for visually-guided object acquisition. The preference for acquisitions concatenates into a preference for unimanual manipulation because the acquiring hand can do many more manipulations (shaking, hammering, squeezing, to-mouth actions, even transfer actions to the other hand) before the non-preferred hand obtains the object. Thus, sensorimotor circuits of acquisition adhere to circuits for acting on the object. Since RDBM requires circuits for one hand's manual exploration of the object while the other hand supports such exploration, we proposed that the acquisition/unimanual object manipulation hand preference would concatenate into a hand preference for RDBM. Several studies provide indirect support for this (Nelson et al., 2013a; Babik and Michel, 2016) but we are currently examining a very large sample of infants to assess the path connection acquisition, unimanual, and RDBM handedness during the period from 6 to 14 months of age.

Additionally, we discovered that the infant's hand preference is affected by the mother's hand preference (Michel, 1992) likely because of the way mothers unintentionally shape their infant's hand use during their dyadic play (Mundale, 1992). As have others, we noted that left handed mothers do not use their left hand in a mirror image of the frequency and character of the use that right-handed mothers make with their right hand. Indeed, whereas right-handed mothers can be strikingly dominant in their use of their right hand, left-handed mothers merely show a moderate bias in their left-hand use. This means that infants who are developing a left-hand preference (based upon their head orientation preference) who have right-handed mothers (a likely occurrence because right-handedness predominates in the population) will have their left-hand preference unintentionally weaken by their mother's hand use during dyadic play. Similarly, infants developing a right-hand preference will have their right-hand use strengthened by their right-handed mothers.

In contrast, infants who are developing a right-hand preference (most infants) will very likely not have left-handed mothers, but if they do, their dyadic play will only mildly affect the infant's right preference because left-handed mothers are not as strongly handed as are right-handed mothers. Of course, infants with left-handed mothers who are developing a left-hand preference because of their left head orientation preference will have their left-hand use strengthened by dyadic play with their left-handed mothers. However, their left hand preference will not be strengthened as much as infants who are developing a right preference with their right-handed mothers. Thus, parental interaction (or indeed, societal proscriptions) can affect the development of the hand preference during and after infancy.

Although some of our studies may have been underpowered and may have generated controversy (but not failures to replicate), we felt comfortable in our assessment of the development of infant hand preferences as a cascading process. Therefore, we began to examine the relation of such development to the development of other cognitive functions. We (Kotwica et al., 2008) observed that a hand preference for acquisition facilitated the development of object storage skills (an ability considered to reflect early symbolic knowledge, Bruner, 1973). Also, an acquisition hand preference predicted advanced language skills a year later at 2 years of age (Nelson et al., 2013b). Consistency of a hand preference across infancy (6–14 months) and toddlerhood (18–24 months) predicted advances in language skills at 3 years of age (Nelson et al., 2017). An infant hand preference predicted advances in infant and toddler object construction skills (i.e., stacking blocks) that is thought to both reflect and contribute to the development of spatial knowledge (Marcinowski et al., 2016).

These predictive relations are only suggestive of an influence of infant hand preference development on cognitive development. Moreover, there have been proposals that infant hand preferences are tied to developing postural control and hence are not consistent during early development (Corbetta and Thelen, 2002; but see Babik et al., 2014; Campbell et al., 2017). Also, infant preferences have been argued to be unrelated to later childhood and adult hand preferences (Dubois et al., 2009). To further confuse the issue, there is some evidence (Esseily et al., 2011, but see Cochet et al., 2011) that infant hand preferences when engaged with objects is not related to their hand preference for the gestural communication skill of pointing. Unfortunately, many of these contradictory studies come from underpowered studies with statistically indefensible classifications of hand preference and too few instances of data collection needed to identify longitudinal trajectories in either hand preference or the cognitive/communication skill examined (Campbell et al., 2015b). This has prompted me to sketch the ideal design for studies that would effectively reveal whether there is any relation between infant/toddler hand preferences and the development of cognitive abilities such as language skills, gestural communication, spatial knowledge, problem-solving, and tool construction and use.

The remainder of this paper will sketch out this design with full recognition that no agency would fund it and that it would take at least two decades to complete (unless multiple labs undertook simultaneous identical investigations to permit achievement of the needed sample size). The power of this design derives from its ability to address most of fundamental problems associated with the investigation of the relation of the development of infant hand preferences to cognitive development.

THE IDEAL DESIGN (A SKETCH)

The examination of the developmental relation between any two psychological functions or skills requires two essentials: (1) the investigator's ability to adequately, appropriately, and reliably (AAR) describe hand preference and the cognitive ability of interest across a developmental period; (2) the investigator's ability to collect longitudinal data that can identify developmental trends in the expression of each function or skill. For the most part, the investigation of the relation of hand preferences to any cognitive function or skill (e.g., language, problem-solving, spatial understanding, numerical skills, tool-use, and artifact construction skills, etc.) has been conducted in a rather *ad-hoc* manner.

For example, when examining the question of whether an infant's hand preference is related to either development of gestural communication or a hand preference in gestural communication, a study may be designed which examines infant hand preference on some task (or using some assessment technique) at a particular age (or across a few ages, seemingly selected by convenience rather than by interest in identifying continuity or change in the hand preference during this developmental period) and the results are compared to the data collected from the same infants using an some assessment of gestural communication (pointing) or of a hand preference for gestural communication. Similar designs have explored infant hand preference and language (production and reception), tool-use, spatial skills, etc. A relation may or may not be observed but little is offered about how these functions (development of a hand-preference and development of the cognitive function) should identified and specified and how best their developmental relation should be examined. Both of these functions require AAR descriptions across longitudinal designs.

ADEQUATE, APPROPRIATE, AND RELIABLE (AAR) DESCRIPTIONS ACROSS DEVELOPMENT

For investigating the relation between hand preference and cognitive functions, this question bifurcates into: Are there AAR developmental descriptions of infant hand-preferences? Are there AAR developmental descriptions of the cognitive functions of interest (e.g., gestural communication, tool-use, artifact construction, spatial language skills, etc.)? Since many of the design characteristics that are essential for AAR descriptions of hand preference development may be applied to the developmental descriptions of other cognitive and sensorimotor skill, this paper will simply focus on the study of hand-use preferences with occasional references to the development of other abilities.

What would be an AAR for assessment of infant hand preferences? No assessment of an infant's ability could capture all the variability both within and among individuals during the development of any cognitive skill. It has long been noted (Annett, 1964) that adult handedness is continuously distributed (as assessed by either performance measures or questionnaire) across individuals despite our common tendency to classify people into discrete categories. A continuous variable with a right skew can only be categorize into classes using statistically defensible criteria. Self-assignment would not be defensible because performance differences and/or answers to questions may be strikingly different between individuals using the same self-assigned class. Moreover, the individual has a lifetime to establish, perfect and manifest a hand preference; any assessment can only reveal snapshots of that process.

We have shown that the preference from birth to 2 years of age must be examined across several manual actions [arm-swiping at visual objects, manually contacting, and acquiring seen objects, manipulating objects with one hand (banging, shaking, tapping, fingering, etc.)], manipulating objects with both hands but in a manner of role-differentiated bimanual manipulation (RDBM). RDBM requires that one hand facilitates the actions the other hand. Thus, the supportive hand enables exploration of the features of the object by the preferred hand or the supportive hand steadies the object while the preferred hand stacks an object on it or uses a tool to alter the object (chipping stone-tools, tying arrowhead to spear shaft). Note that most adult hand preferences are manifest during RDBM actions.

Hand preferences for these infant manual actions become manifest at different ages (swiping from 2 to 5 months, acquisition from 5 to 14 months, unimanual manipulation from 9 to 12 months, RDBM from 12 months to?). Thus, an appropriate assessment during infancy would have to include separate assessments of hand preferences for each of these actions because these are characteristic examples of the types of manual actions in which a hand preference may be exhibited. The assessment would be adequate if it included enough instances of each type of action to estimate the probability that any preference exhibited in the action would be unlikely to occur by chance. The assessment task should be reliable in that re-assessment within the same age does not alter the infant's apparent preference. Of course, the preference is likely to show a somewhat continuous character in the frequency of each hand's use across assessments and individuals, but it should be possible to statistically identify potential preferences that fit three general categories of right, left, and no statistically reliable preference. With a large enough sample size, the sample may be divided further (statistically) to reveal additional sub-groupings (those developing a preference earlier than others) within these three general categories.

Therefore, AAR assessment of infant handedness would require a large sample with testing that would have to be conducted across a 2+ decades. Evidence from published studies suggest that a sample of 400 (in rolling cohorts of about 40 longitudinally examined across their first 3 years and tested once again at 5 years of age) would provide some 60+ infants who are likely to exhibit a leftward HOP during their first 10 neonatal weeks, most of whom would likely develop a later left-hand preference and about 80+ would have no reliable preference for either HOP or hand-use. These sample sizes would permit reliable estimation of the relation of a left or right preference relative to no preference for the development of any cognitive ability.

More importantly, this sample would permit experimental manipulation of manual feedback influences on the asymmetry of neural monitoring of each hand created by the HOP. For example, using a variant of Needham's "sticky mittens" procedure, each of the three HOP groups (identified by three assessments of the HOP at 3, 6, and 9 weeks postpartum) would be divided into three groups: those who would have no mittens experience but be exposed to the testing procedures, a group who would have mittens on both hands, and a group who would have mittens on their "face-side" hand as determined by the HOP. For those infants without a HOP, a third (about 25–30 infants) would be randomly assigned a mitten hand. The mittens are worn for a week starting at 12 weeks' post-partum and their swiping at objects and their evoked potentials to vibrational stimulation of their fingers on their right and left hands would be tested before and after the week of sticky mitten experience.

If the asymmetrical feedback from HOP has an influence on neural circuits associated with control of the arms/hands, then before the sticky mitten manipulation, both the right and left HOP infants should exhibit greater evoked potentials (EPs) to stimulation of their face-side hand than their skull-side hand and there should be no differences among the infants without a HOP. After sticky mitten experience, the asymmetry in the EPs should be greater for those infants with a HOP and there should be an asymmetry apparent for those infants without an HOP but who had the asymmetrical sticky mitten experience. If there is no asymmetry of EPs associated with HOP or sticky mitten experience, then it is possible that the sticky mitten experience does not create the feedback common for the construction of the asymmetric circuits in the brain or it is possible that the asymmetric monitoring of the hands created by the HOP (and enhanced by the sticky mitten experience) does not help sculpt neural circuits involved in hand control. These results would provide an answer to the basic question of whether the infant's neural development is, in part, shaped by its own self-generated experiences.

The assessment of HOP at only three ages does not permit description of the developmental trajectory of HOP. However, the assessment or hand preferences (for acquisition, unimanual, RDBM actions) every 2 months from 5 to 25 months (11 assessment periods) permits replication of our published developmental trajectories for hand preferences for acquisition and unimanual manipulation. Also, it permits identification of the developmental trajectory of hand preference for RDBM from 11 to 25 months (8 assessment periods). This latter data enables us to connect the first year RDBM hand preferences to RDBM hand preferences in the second year and estimate their developmental trajectories. Moreover, collection of data on construction skills (e.g., stacking), tool-use, and pointing conditions from 11 to 25 months would provide sufficient data to identify trajectories in the development of these abilities as well as hand preferences within each.

Of course, identifying hand preferences in these sensorimotor skills requires enough instances of the manual actions manifest in each to reliably eliminate chance in any apparent hand preference. Thus, for a hand preference for pointing, there would need to be at least 15 and better 20 instances of unimanual pointing for each age period. These same infants can be tested bimonthly from 23 to 35 months of age (7 assessment periods) on various specific language skills (e.g., the use of spatial prepositions) and a common preschool hand preference task (Scharoun and Bryden, 2014) could be administered at 33 and 35 months of age. The latter could reveal how well measures of hand preference in early infancy predict later hand preferences and how these later preferences relate to concurrent language ability.

For a more conventional measures of language development, the MacArthur Communicative Development Inventory (MCDI) could be collected around the ages for hand preference assessment. The MCDI provides a caretaker assessment of language development with an infant component useful from 8 to 16 months postpartum and a toddler component useful from 16 to 30 months. In contrast, another conventional language assessment task, the Preschool Language Scale (PLS-5), is an experimenter administered assessment that can be conducted in a lab or home setting and could provide standardized measures of the child's language skills at two and three years of age. Both these assessments could be compared to previous and concurrent measures of hand preference.

It is easy to extrapolate from the assessment of language skills to the assessment of any other cognitive skill for this age range. So, this design Sketch has some general developmental utility. By itself, it can elucidate the relation of hand preference development with object manipulation to the hand preference exhibited during gestural communication. The design could reveal also whether the assessment of infant hand preferences relate to hand preferences exhibited in construction actions and tool-use as well as developmental advances in these skills relative to infant hand preferences. The design permits identification of whether infant and toddler hand preferences relate to common assessments of preschool hand preference (see **Tables 1A,B** for a sketch of some of the tasks and hypotheses that could be tested with this longitudinal assessment design. Note that it would be easy to include additional cognitive, social and emotional tasks at additional ages to assess the effects of handedness on the development of these abilities and certain aspects of embodiment theory).

Moreover, if these children can be examined again at 5 years of age, they could be given school readiness tests, children's handedness assessments, and some common cognitive tasks that could be related to their concurrent and earlier collected

TABLE 1A | Tasks and hypotheses tested during infancy ($n = 400$).

Age	Tasks	Hypotheses tested
3, 6, 9 Weeks Postpartum	Assessing Head Orientation Preference (HOP)	Does HOP affect lateral asymmetries in self-touching and arm and hand movements?
12, 15, 18 Weeks	1 week of sticky mitten experience at 12 weeks (4 Groups: Face side hand only, both hands, non-sticky mittens)	Is there greater swiping at objects with face side hand and more so after wearing sticky mitten?
	ERPs from contralateral vibration of fingers of left and right hands	Does face side hand stimulation provokes greater ERP than skull side hand; Does hand that wore sticky mitten provokes greater ERP than face side hand alone; Does earlier HOP should predict hand used most frequently when swiping at objects at 18 weeks?
10, 12, 14, 16, 18, 20 Months	Role Differentiated Bimanual Manipulation (RDBM	What is the pattern of development of hand preference for RDBM; Does earlier HOP and swiping hand preference predict hand preference for RDBM?
	Pointing	Does RDBM hand preference predict developmental trajectory of pointing; a hand preference for pointing?
	Tool-use	Does RDBM hand preference predict developmental trajectory of tool-use; a hand preference for tool-use?
	Object Construction	Does RDBM hand preference predict developmental trajectory of construction skills; a hand preference for construction?
	MacArthur-Bates Communicative Development Inventory (MCDI)	Does RDBM hand preference predict developmental trajectory of language skills?

TABLE 1B | Tasks and hypotheses tested during preschool years ($n = 400$).

Age	Tasks	Hypotheses tested
24, 30, 36, 48 Months	Preschool Language Scale-–5th Edition (PLS-5)	Does infant RDBM hand preference predict earlier development of language skills?
	Scharoun and Bryden Handedness Assessment	Does infant RDBM hand preference predict development of child hand preference assessment; Does child hand preference predict concurrent language skill?
	RDBM Handedness Assessment	Does RDBM hand preference remain stable during early childhood; Does child RDBM hand preference predict concurrent language skill; what is the relation between the two hand preference assessments?
	Theory of Mind (ToM) Tasks	Examine relation of handedness to ToM; Do infant hand preferences predict differences in ToM development; Do current hand preferences predict differences in ToM development?
60 Months	School Readiness Test-–4th Edition (SRT-4)	Do infant and child assessments of hand preference predict differences in SRT performance?
	Bender Gestalt Copy Designs Test (BGT)	Do infant and child assessments of hand preference predict differences in copy design performance?
	Scharoun and Bryden Handedness Assessment	Do child hand preferences predict hand preferences at 5 years?
	RDBM Handedness Assessment	Do infant and/or child hand preferences for RDBM predict hand preferences at 5 years?
	Theory of Mind (ToM) Tasks	Examine relation of ToM to SRT and BGT

hand preference and language data. Two+ decades of such intensive data collection and analysis could provide the most AAR data on the relation of early hand preference development to various language and other cognitive skills. Moreover, it would set the investigation of early psychological development on a path that requires programmatic, longitudinal, large sample research designs that could only improve our understanding of psychological development.

CONCLUSION

There is growing theoretical interest in, and experimental support for, various forms of embodiment theory of cognitive development. Clearly, a hand-use preference is the most common and distinctive source for the formation of differences in embodied sensorimotor actions. Hand preference differences during infancy and toddlerhood would matter in profound ways for things like object exploration, artifact construction, and tool use. How one holds the object and what infants see of the object as they engage in manual actions is going to differ. The information infants collect and possibly how/if they engage with another person around these activities could be different depending on their hand preference. Therefore, differences in cognition across handedness groups is a good test of certain forms of embodiment theory (Casasanto and Henetz, 2011).

Since there is much evidence that the development of left-hand preferences is not the mirror image of the development of a right-hand preference, sample sizes need to be very large to have the power to identify whether a hand preference or a specific (left or right) preference directly relates to the development of any cognitive ability. Although certain forms of embodiment theory predict that a hand preference ought to relate to many cognitive abilities, the effects of the difference in the development of a left verses a right preference must be examined because they, too, ought to create differences in cognitive ability. I propose that investment in the collection via the design sketched here would provide greater payoff than continued investment in the more *ad-hoc* projects.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board for the protection of human subjects of the University of North Carolina Greensboro with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the UNCG IRB.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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ORIGINAL RESEARCH
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Unique Neural Characteristics of Atypical Lateralization of Language in Healthy Individuals

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Using functional magnetic resonance imaging (fMRI) in 63 healthy participants, including left-handed and ambidextrous individuals, we tested how atypical lateralization of language—i. e., bilateral or right hemispheric language representation—differs from the typical left-hemisphere dominance. Although regardless of their handedness, all 11 participants from the atypical group engaged classical language centers, i.e., Broca's and Wernicke's areas, the right-hemisphere components of the default mode network (DMN), including the angular gyrus and middle temporal gyrus, were also critically involved during the verbal fluency task. Importantly, activity in these regions could not be explained in terms of mirroring the typical language pattern because left-hemisphere dominant individuals did not exhibit similar significant signal modulations. Moreover, when spatial extent of language-related activity across whole brain was considered, the bilateral language organization entailed more diffuse functional processing. Finally, we detected significant differences between the typical and atypical group in the resting-state connectivity at the global and local level. These findings suggest that the atypical lateralization of language has unique features, and is not a simple mirror image of the typical left hemispheric language representation.

Keywords: language, handedness, left-handers, connectivity, specialization, laterality, resting-state fMRI, verbal fluency

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INTRODUCTION

The lateralization of language is a hallmark of the brain's functional architecture. This cerebral characteristic manifests itself, for example, in that nearly 90% of right-handers use predominantly their left hemispheres during language production (Knecht et al., 2000a). Yet, a substantial number of individuals, particularly left-handers, demonstrate bilateral or even right hemispheric language representation (Knecht et al., 2000b). In accordance with some accounts, the most vivid consequences of such atypical hemispheric specialization may include various kinds of language deficits, e.g., stuttering (Fox et al., 2000). Although, much has been established about the organizational factors contributing to such deficits, very little is known about the neural underpinning of atypical lateralization of language in healthy individuals. Importantly, it is still unclear to what extent atypical language laterality is a mirror image of the typical left-hemispheric dominance.

In clinical populations, atypical, i.e., bilateral or right-hemispheric, representations of language have been linked to early injuries to the left hemispheres or epilepsy (Rasmussen and Milner, 1977).

It has been widely assumed that such lesions, or even deficiencies in blood flow, particularly the ones affecting the Broca's and Wernicke's area, induce inter-hemispheric language reorganization leading to an atypical functional dominance (Lazar et al., 2000). Furthermore, on the basis of symptom similarities between children with acquired brain injuries and left-handed aphasics a hypothesis was proposed that manual preference also affects language organization, i.e., right-handedness facilitates, and left-handedness hinders the process of establishing the typical left hemispheric dominance for language (Brown and Hecaen, 1976). Finally, given the hypothesis that right hemisphere representations of functions are more diffused (Semmes, 1968), a prediction was put forward that atypical laterality should be reflected in a less focused language representation, and would occur particularly in children with an early brain injury, and in left-handers (Bishop, 2013). In sum, there is evidence from clinical populations suggesting that atypical language laterality differs from the typical representation of this function in terms of etiology and more diffused spatial distribution.

The studies investigating crossed aphasics, i.e., right-handed individuals with aphasias after right hemisphere damages, pointed, however, to quite focused contributions of the right hemispheres to language functions (Henderson, 1983; Basso et al., 1985; Alexander et al., 1989; Marien et al., 2004). Indeed, the putative representations may have even mirrored the typical organization observed in the left hemisphere, indicating that the intra-hemispheric organization of language does not depend on the side of functional dominance (Henderson, 1983). Furthermore, investigations of large groups of left-handed aphasics (Goodglass and Quadfasel, 1954; Hecaen and Sauguet, 1971) have demonstrated that in most of the cases language was lateralized typically to the left hemisphere, as in right-handers. Likewise, when right-handed aphasics were matched with left-handed aphasics with similar size and side of the lesion, education, age, length of illness, etiology, and sex, almost no differences in their aphasia profiles were found (Basso et al., 1990). Therefore, it has been suggested that a presumed link between manual preference and cerebral lateralization is in fact not mandatory (Goodglass and Quadfasel, 1954; Hecaen et al., 1981). All in all, the current interpretation of the wide range of neuropsychological evidence indicates that atypical right hemisphere language lateralization is neither diffuse nor exclusively associated with left-handedness (see also Schmitz et al., 2017), with the link to an early brain injury being doubtful, and no clear indication that it simply mirrors the one present in the left hemisphere.

With the advent of neuroimaging methods, hypotheses related to the atypical representation of language could be verified with greater anatomical precision, and thus could potentially extend or even revise our knowledge on this matter. Indeed, the patient population studies which used functional magnetic resonance imaging (fMRI) suggest that the majority of the atypical individuals exhibit a mirror image representation of the classical language centers (Staudt et al., 2002; Tivarus et al., 2012). However, there is also evidence that some individuals demonstrate intrahemispheric reorganization in the language network which manifests itself by the engagement of the left temporal lobe areas that is not observed in the typical individuals (Mbwana et al., 2009). Moreover, there is also some evidence (Voets et al., 2006) that peaks of activities within the Broca's area are not homologous. Specifically, patients with atypical laterality had the average peak of activity on the right located significantly more posteriorly than typical individuals.

Studies in healthy population support main findings from patients. Mirror-image language representations were found in right-handers in the small-scale study by Knecht et al. (2003), and not surprisingly in a large cohort of left-handed individuals by Tzourio-Mazoyer et al. (2016). There is also evidence that the atypical laterality is related to increased bilateral temporal lobe activity, an observation that suggests potential intrahemispheric reorganization (Tzourio-Mazoyer et al., 2016). Furthermore, the latter study also demonstrated that greater inter-hemispheric resting-state connectivity in homotopic regions connected via the corpus callosum is related to reduced lateralization of task-related activity (see also a review by Tzourio-Mazoyer and Seghier, 2016). These results, together with the analyses of behavioral data on atypical laterality of functions (e.g., Michałowski and Kroliczak, 2015) point to an exciting possibility that the left- and right-hemispheric language systems—despite yielding the same outputs—have in fact different connectivity with other brain networks. This issue can be approached by the analyses of location of the peaks of activity within homologous IFG subdivisions, an approach that none of the above studies adopted. If such differences exists, the right lateralized language system would not necessarily be a mirror version of its left-hemisphere counterpart, but a unique representation of this function (Price and Friston, 2002).

A support for this proposal comes from recent task-based fMRI studies which showed that a greater engagement of the Broca's area counterpart in the right hemisphere during word generation is often associated with atypical activity of regions involved in word reading (Cai et al., 2010), gesture planning (Kroliczak et al., 2011), and visuospatial processing (Cai et al., 2013). These functional regularities are also accompanied by changes in the structure of the brain, particularly in the insular cortex (Keller et al., 2011; Biduła and Kroliczak, 2015), and Heschl's gyri (Tzourio-Mazoyer et al., 2015). Based on this evidence, atypical language organization would be a consequence of substantial alterations in the structural and functional architecture of the cerebral cortex (e.g., Biduła and Kroliczak, 2015; Michałowski and Kroliczak, 2015). Such changes should be also apparent in functional connectivity, which in turn may constrain the brain's architecture (Stevens et al., 2015), leading to a very distinct pattern in individuals with atypically lateralized language.

In this way language lateralization could be seen as a factor which, depending on the initial structure of the cerebral cortex, substantially affects later structural and functional plasticity, as well as intrinsic and resting state connectivity. In particular, the influence of language laterality should be seen in the default mode network (DMN; Mazoyer et al., 2001; Raichle et al., 2001; for a recent review see also Raichle, 2015), which shares an intimate relationship with the semantic aspects of language (Binder et al., 1999). Notably, a recent study (McAvoy et al., 2016) showed that this link between default network and language lateralization could be observed even at the level of the hemispheric resting-state global signals. Therefore, it is worth to include these, often discarded, signals in the analyses of the alterations related to the language organization in heathy individuals.

In this study, we asked whether or not atypical hemispheric language organization differs from the typical representation of this function. To address this question, we tested 63 healthy individuals using fMRI. Language lateralization was measured with the verbal fluency task, and functional connectivity was assessed with the resting-state scans. Although, we found that atypical language organization mirrors, to some extent, the typical one observed in the left hemisphere, it differs substantially in the spread of cortical activity, as well as in the pattern of functional connectivity. Moreover, these results clarify the putative relationships between manual preference and language organization by showing that left-handed participants with a typical language organization did not differ from right-handed individuals who also exhibited typical, left-hemispheric language laterality. Taken together, our results provide a detailed picture of changes in the brain related to atypically organized language faculty, and suggest that such atypical asymmetry is a natural yet unique representation of function.

MATERIALS AND METHODS

Participants

Sixty-three healthy individuals (32 females/31 males; mean age ± standard deviation = 22.5 ± 3.4 years; median = 22; range = 19–39) volunteered to take part in this study. All participants were native speakers of Polish, and their handedness was assessed with the revised Edinburgh questionnaire (Oldfield, 1971): 28 of them were right-handed, 21 left-handed, and 14 were ambidextrous. Scores of +40 and above in the questionnaire indicate right-handedness, scores of −40 and below denote left-handedness, and the results in between signify ambidexterity (see Whitehouse and Bishop, 2009). A large sample of non-right-handers was on purpose included because they tend to have atypical lateralization of language (Knecht et al., 2000b; Kroliczak et al., 2011), which was a crucial premise for our study (see also Willems et al., 2014). All students who self-identify themselves as non-right-handers were encouraged by adds in the local papers, social media, and other flyers to take part in this study. After they voluntarily decided to participate, the revised Edinburgh questionnaire was administered to verify their opinions about their handedness. All non-right-handed volunteers with no contraindications for fMRI testing were included to increase heterogeneity of manual preference scores and, therefore, to omit the "restriction of range" problem in the correlation analyses. Some ambidextrals (3 participants) were truly bimanually skilled, because when they were recruited from the *Academy of Music in Poznan* (http://amuz.edu.pl/), we made sure they were proficient in playing instruments that required using both hands. None of the participants had any history of neurological or psychiatric disorders. In particular, care was taken to ensure that none of the studied individuals had any early brain injury or language impairment. Each participant provided written informed consent for voluntary participation in this study (which was a part of a greater project, e.g., Przybylski and Kroliczak, 2017), whose procedures were reviewed and approved by the Bioethics Committee at Poznań, University of Medical Sciences (Ethical Approval No. 63/12). Hence, the study methods were consistent with the principles of the 2013 World Medical Association Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/).

Verbal Fluency Paradigm

To assess language laterality, we asked our participants to perform a cued verbal fluency task. In nearly all subjects, the experiment was carried out twice, in 2 different scanning sessions and on 2 consecutive days. This procedure was administered to increase the signal-to-noise ratio of the analyzed images. The test consisted of six 30-s task blocks, alternated with 30-s periods of rest. During task-related functional epochs, participants were required to silently generate as many words as possible beginning with a particular letter (i.e., L, M, G, K, T, or A) presented visually above the fixation cross. The letters used in this task were chosen based on the Corpus studies of the Polish language, which showed that most of the words that people spontaneously use begin with such letters.

Resting-State Paradigm

To assess functional connectivity, two resting-state scans were acquired in most of the individuals during the same sessions as the verbal fluency test. Resting-state fMRI is based upon an observation that spontaneous activity of the brain is highly structured (for a review see Murphy et al., 2013; Power et al., 2014b). Indeed, during rest distinct cerebral areas exhibit coherent signal modulations that form reproducible patterns (Damoiseaux et al., 2006), similar to those demonstrated during a specific task (Smith et al., 2009). Such connectivity patterns are constrained by the underlying anatomy (Greicius et al., 2009), yet could also be used to study polysynaptic neuronal circuits (Vincent et al., 2007).

In our study, during resting-state scans participants laid inactive for 6 min, a centrally presented fixation cross helped them not to move their eyes, they were instructed to think of nothing in particular, and not to fall asleep. The requirement of maintaining fixation was adopted because a substantial number of subjects during resting-state scans with their eyes closed drifts between wakefulness and sleep, which is likely to alter the functional connectivity (Tagliazucchi and Laufs, 2014). Moreover, it was shown that resting-state networks observed when individuals fixate on a cross are the most reliable (Patriat et al., 2013), and give the greatest effect sizes (Van Dijk et al., 2010).

Imaging Parameters

Imaging was performed at the Laboratory of Brain Imaging in the Nencki Institute of Experimental Biology with Siemens (Germany) 3 Tesla TRIO MRI scanner equipped with a 32-channel head coil. The blood oxygenation level-dependent (BOLD; Ogawa et al., 1990) T2*-weighted gradient echo planar images (EPI) had the following parameters: time repetition (TR) = 2,000 ms; time to echo (TE) = 30 ms; flip angle = 90°; 64 × 64 matrix; field of view (FOV) = 200 mm; 35 axial slices, 3.1-mm isotropic voxels, were acquired as a proxy to study neural responses. For detailed anatomy, in each participant, we obtained standard T1-weighted images with magnetization prepared rapid gradient echo (MP–RAGE; Mugler and Brookeman, 1990) pulse sequence: TR = 2,530 ms; TE = 3.32 ms; inversion time (TI) = 1200 ms; FA = 7°; 256 × 176 voxel matrix size; FOV = 256 mm; 176 contiguous axial slices; 1.0-mm isotropic voxels). To enhance the precision of registration between EPIs and T1-wighted images we also acquired fast spin echo SPACE (sampling perfection with application optimized contrasts using different flip angle evolution) T2-weighted structural images with the following parameters: TR = 3,200 ms; TE = 402 ms; FA = 120°; 512 × 512 voxel matrix size; FOV = 256 mm; 176 contiguous sagittal slices; 0.5-0.5-1 non-isotropic voxels. The obtained DICOM files were converted to NIFTI-1 format (http://nifti.nimh.nih.gov/nifti-1) using MRI-Convert software (http://lcni.uoregon.edu/jolinda/MRIConvert/).

Structural Imaging Data Analyses

Structural, i.e., T1- and T2-weighted, images were analyzed using FreeSufer v5.3 (Fischl, 2012), and FSL v5.0.6 (Jenkinson et al., 2012). First, MP–RAGE scans were averaged using FSL FLIRT (*flirt_average*) because in the vast majority of studied individuals (61) two such images were obtained. The resulting images were then processed with *recon-all* procedure available in the FreeSufer package. In short, this routine computes transformation to the Talairach atlas (Talairach and Tournoux, 1988), corrects signal inhomogeneity (Sled et al., 1998; Zheng et al., 2009), and extracts the brain (Segonne et al., 2004; Sadananthan et al., 2010). Next, non-linear atlas registration is computed, the neck is removed, and white matter is segmented. After dividing the hemispheres, the gray matter/white matter boundary is tessellated, and automated topology correction is applied (Fischl et al., 2001; Segonne et al., 2007). The obtained cortical reconstructions are then spherically registered to the fsaverage atlas (Fischl et al., 1999a,b; Buckner et al., 2004). The results of subcortical brain segmentation and overall brain size were used to test specific hypotheses related to these variables.

Skull-stripped and bias-corrected images (brain.mgz) were back projected to their native size (rawavg.mgz) and segmented into three classes, namely the gray matter, white matter, and cerebrospinal fluid using FSL FAST (Smith et al., 2004). The resulting tissue masks were then thresholded, binarized, and resampled to the resolution of resting-state EPI images. Matrix for this operation was computed using the boundary-based registration (Greve and Fischl, 2009) implemented in the FSL package (*epi_reg*).

Verbal Fluency Imaging Data Analyses

The following preprocessing procedures were applied to the functional language data before statistical analyses: (1) non-brain tissues were removed using brain extraction tool (BET; Smith, 2002); (2) head motion during the scan was corrected with MC-FLIRT (motion correction with the FMRIB Linear Image Registration Tool; Jenkinson et al., 2002) by maximizing the correlation between each volume and the reference time-point (middle volume); (3) images were spatially smoothed using a Gaussian kernel of full width half maximum (FWHM) = 6.2 mm to reduce noise; (4) intensity of all volumes was normalized using mean-based method, and finally (5) images were temporally smoothed using high-pass filtering ($\sigma = 50.0$ s). For a given subject, each fMRI run was analyzed separately at the first level. Before statistical analyses, autocorrelation in the data was corrected using prewhitening procedure (Woolrich et al., 2001). Hemodynamic response was modeled using the double-gamma function. The single subject analyses were conducted in the native space of the studied individual. Runs from a given participant were averaged using fixed effects model implemented in FSL Feat. Intersubject analyses were, on the other hand, performed utilizing random-effects components of mixed-effects variance available with FLAME Stage 1 and 2 (Beckmann et al., 2003). These group analyses were performed in the normalized MNI-152 space (voxel size 2 × 2 × 2 mm). The resulting Z (Gaussianized t/F) statistic images were thresholded using Z-value of 3.1 and corrected for multiple comparisons using clusterwise significance threshold of $P = 0.05$ (Jezzard et al., 2003; Eklund et al., 2016). Notably, the clusterwise method of thresholding images does not set-up a minimal size or number of interconnected voxels but, instead, calculates the distribution of the largest cluster within the analyzed image, after initial thresholding at a particular Z-value. Based on this, a family-wise threshold is subsequently applied. Initial explanatory analysis was carried out using a more lenient, traditional threshold of $Z > 2.3$. Peaks of activity resulting from this investigation, specifically from a comparison of verbal activity between typical and atypical group, were used in the resting-state analyses.

Spatial normalization was performed in a series of steps using FLIRT with default cost function and interpolation method (Jenkinson and Smith, 2001). First, EPIs were aligned with T2-weighted structural images with 6 degrees of freedom (DOF). Next, T2- and T1-weighted images were registered to each other with 7 DOF. Finally, MP-RAGE scans were warped to the atlas space (Montreal Neurological Institute [MNI-152] template 2 × 2 × 2 mm) using affine transformation (12 DOF).

Laterality Measurements

Laterality index for each study participant was measured in a manner similar to Jansen et al. (2006). Specifically, a mean of 5% of voxels showing maximum activation value in one of the paired ROIs was calculated first. Then, uncorrected Z map was thresholded at 50% of this mean maximum activation value. Voxels that survived this thresholding were entered to the following equation: $LI = [(L - R)/(L + R)] * 100$, where L represents voxels that survived thresholding in the left ROI, and R denotes voxels that survived thresholding in the right ROI. A score of +100 indicates complete left hemispheric dominance, −100 complete right hemispheric dominance, and a score between 33 and −33 implies bilateral organization of language function (see Kroliczak et al., 2011).

This laterality measurement method addresses the problem of outliers and threshold dependency in a simple manner. More sophisticated procedures, such as a popular among SPM users toolbox (Wilke and Lidzba, 2007), instead of calculating the mean of 5% of voxels showing maximum activation value, use histogram analyses and the threshold problem is resolved by using a bootstrap algorithm. In an approach preferred by us (Jansen et al., 2006), thresholding at an individually adjusted level is used. Notably, we also went on and used other methods for assessing individual laterality. For example, we verified our initial participant classification based on LIs using a graph analysis (see below).

Laterality indices were measured in the Broca's area, which is one of the landmark structures of verbal fluency (Adcock et al., 2003). This area was defined by means of the probabilistic cytoarchitectonic maps implemented in the FSL package, as Brodmann areas (BA) 44 and 45 (Amunts et al., 1999). Specifically, left and right masks of each BA were thresholded at 50% of their maximum probability, added, and binarized. The left BA 44/45 mask has the size of 2,119 voxels (16,952 mm^3), whereas the right one has the size of 1,581 voxels (12,648 mm^3).

Region of Interest Analysis

To test whether or not peaks of verbal activity within the Broca's area are located in similar anatomical locations across groups we performed a region of interest analysis. Specifically, we once again ran the average analysis for the verbal fluency test for each individual separately. However, this time this analysis was limited to the confines of the Broca's area mask used in the LI measurements. This procedure resulted in a peak of activity for each individual, which we defined as a voxel with the highest Z-score. Atlas coordinates of those points were compared using the t-test. Importantly, by using this method we were able to find a peak of activity even for a participant with bilateral representation of language. Nevertheless, as we were interested in clarifying whether atypical group has right hemispheric peaks of activity located more anterior/posterior, and/or superior/inferior to group with typical language organization, we contrasted these groups across y- and z-coordinates. One participant, who was classified as atypical—bilateral, exhibited the peak of activity in the left hemisphere. He was therefore excluded from the group comparison.

Graph Analysis of the Verbal Fluency Neural Patterns

To analyze the patterns of language lateralization among our participants we applied the procedure based on *3ddot* function from the AFNI suite. This allowed us to calculate spatial correlations between each unthresholded Z-stat image for the verbal fluency test. As before, this analysis was limited to the Broca's area defined by the same mask that we used to measure the LIs. The resulting 63 × 63 matrix entered Gephi 0.9.1 program and was turned into a graph. The matrix on which the graph is based represents Pearson spatial correlations between all voxels within the unthresholded Z-stat images from the task. The analysis was limited only to the Broca's area, namely, it was performed within the confines of the BA44/45 ROI, previously used in the LI assessment. Subsequently, the program's modular algorithm task was to detect distinct groups of neural patterns in the analyzed spatial relationships depicted by the graph (Blondel et al., 2008).

Resting State Imaging Data Analyses

Resting-state imaging data were analyzed using AFNI v1.8 (Cox, 1996, 2012), and FSL v5.0.6 (Jenkinson et al., 2012) packages. First, extreme values in the raw data time-series were removed (*3dDespike*), and misplacements between volumes due to between-scan head movements were corrected (*3dvolreg*). Next, MR signal intensity in the brain was normalized to a global mean of 1000 (*fslmaths*). Then linear trends were removed (*3dTcat*), and temporal bandpass filter ($0.01\,\text{Hz} < f < 0.1\,\text{Hz}$) was applied to the data time-series (*3dFourier*). Similar bandpass filter was also used to temporally smooth motion parameters obtained in the motion correction step (*1dBandpass*). After these procedures were completed, spurious variance, not related to neuronal processing, was removed by nuisance regression of the following signals: 24 motion related waveforms, signal related to the cerebrospinal fluid (and its backward difference), and time-series from the white-matter mask (also with its backward difference). Global signal was not included in this regression as its removal alters the group-level analyses qualitatively (Murphy et al., 2009), and is possibly related to the functional lateralization (McAvoy et al., 2016). In contrast, we studied hemispheric global signal as a signal of interest using the procedure described below. Finally, images were uniformly smoothed with 6.2 mm FWHM filter within the gray matter mask to reduce noise (*3dBlurToFWHM*). Note that we controlled head motion confounds using two methods, i.e., extended motion regressors (Friston et al., 1996), and uniform smoothing (Scheinost et al., 2014). No motion scrubbing was applied to the data as it disrupts temporal structure of the scan and alters the between-subjects degrees of freedom (Power et al., 2014a).

After initial preprocessing, a comparison between functional connectivity profiles of the group with typical and the atypical language lateralization was conducted. First, spherical masks of 5 mm radius centered on the coordinates of peak group differences (seed regions) from the word generation task were created (*fslmaths*). Then mean time-series were extracted from these masks (*fslmeants*), and the resting-state functional connectivity maps for each seed were calculated (*feat*) using a statistical procedure similar to the analysis of the verbal fluency activity (i.e., fixed effects were used for averaging scans in single subjects and random-effects components of mixed-effects variance were used for inter-subject analyses; $Z > 3.1$; clusterwise significance threshold of $P = 0.05$). Specifically, time courses of each seed, including global signal from the left and right hemisphere, were used as predictors in a multiple regression model at the individual participant level (see Hutchison et al., 2014, who used similar procedures).

Group analyses of the differences between the resting-state hemispheric global signals were performed on contrast images derived from comparing the left-to-right (left > right) or right-to-left (right > left) hemispheric signals from the initial multiple regression without any seed.

Verification of Anatomical Localizations

Anatomical localizations in all analyses were verified using an atlas (Duvernoy, 1991), and probabilistic maps available in the FSL package (Eickhoff et al., 2007). Moreover, to aid sulcal and gyral identification, cortical surfaces and T1-weighted images of each individual were averaged (*make_average_subject*) to create a surface and volume representation of all study subjects' anatomy. Results of our analyses were overlaid on these averaged representations, i.e., average volume and surface. As our average study template was in correspondence with the fsaverage atlas, in which cerebral networks are included (Yeo et al., 2011), we could also identify which cerebral networks, including default mode and ventral attention systems, were altered in participants with atypical language lateralization.

RESULTS

First, we provide a general picture by describing the similarities and differences in brain activity of the groups with typical and atypical language lateralization. Second, we report the results of the seed- and global-based connectivity analyses, which give a more detailed description of alterations related to the atypical language organization.

Verbal Fluency Task vs. Rest Blocks from the Same Test Runs

The brain areas activated in all participants during the verbal fluency task contrasted with the epochs of resting baseline formed widespread networks located in the frontal, parietal, temporal, and occipital cortices, particularly in the left hemisphere. In the frontal lobe, increased activity was found within the left inferior frontal gyrus (IFG), bilateral ventral premotor cortices (PMv), anterior banks of the precentral gyri, the left dorsal premotor cortex (PMd), supplementary motor area (SMA), the middle part of the cingulate cortex (mCC), and bilateral anterior insulae (aI). Notably, in the left parietal cortex we detected significant activity along and within the intraparietal sulcus (IPS). We also observed increased engagement of the left superior temporal sulcus (STS), bilateral inferior temporal gyri (ITG), and fusiform gyri (FG). Likewise, in the occipital lobe substantial activity was observed within the left and right inferior parts of the middle occipital gyri (MOG), as well as in the occipital poles (OP). There were also signal increases detected in the left and right putamen, caudate, and thalamus (Th). Finally, we observed significant signal amplifications within the anterior lobes of the cerebellum. These results are displayed in **Figure 1A** and the peak coordinates of identified clusters are reported in **Table 1**.

Verbal Fluency Task vs. Implicit Baseline

When the BOLD signal during the verbal fluency task was compared with the implicit baseline, i.e., the mean signal from the same test runs, we observed more spatially restricted effects. Specifically, this analysis revealed two circumscribed clusters of significant signal modulations in the left hemisphere. These activity patterns are shown in **Figure 1B**. The first set of areas included IFG, PMv, aI, and ventral parts of the precentral gyrus. The second cluster was located mainly in the vicinity of SMA.

Laterality Measurements

The verbal fluency activity, when contrasted with both resting and implicit baseline, showed a common cluster of lateralized signal modulation mainly in the IFG, i.e., a part of the Broca's area (Keller et al., 2009). Thus, we measured language laterality in this ROI approximated with the BA 44/45 thresholded mask. As anticipated, the vast majority of studied participants (83%) demonstrated quite typical left-hemispheric representations of language during the verbal fluency test as measured in the so-defined Broca's area. Nonetheless, a substantial number of examined individuals still demonstrated a bilateral (9%), or even right hemispheric (8%) lateralization of the studied function within this ROI. Participants that showed atypical language organization (bilateral or right hemispheric) were combined into one group for subsequent analyses. A distribution of laterality indices across all studied individuals is presented in **Figure 2A**.

Considering the earlier reports of the effects of age (Szaflarski et al., 2002), handedness (Knecht et al., 2000b), and sex (Shaywitz et al., 1995) on hemispheric specialization for language, we also examined the potential effects of these factors in our sample. First, there was no significant association between laterality indices and age ($r_{61} = -0.07$, $P = 0.575$), possibly due to the small age-related variability within our group (mean age 22.5 ± 3.4 years). There was, however, a significant impact of handedness on LIs. Specifically, a two (sex) by three (handedness) ANOVA revealed that right-handers were more left lateralized than left-handers ($P = 0.005$). Sex did not influence the laterality measures, as the difference between LIs for females and males was not significant ($P = 0.224$). The relevant distributions of LIs across each group of participants are shown in **Figure 2B** (divided by sex), and **Figure 2C** (divided by handedness).

Handedness and Language Laterality

The above analyses showed that in our sample handedness was the only demographic variable that impacts LIs. Having the possibility to investigate this relationship further, we conducted an additional, independent-samples *t*-test to compare right- and left-handers, but only the ones with typical left-hemispheric language organization, and who participated in both fMRI sessions (and we knew their activity patterns were reproducible). This analysis showed no significant differences whatsoever between right-handers ($N = 25$, $M_{\mathrm{LI}} = 92.2$, $SD = 12.9$) and left-handers ($N = 12$, $M_{\mathrm{LI}} = 88.5$, $SD = 16.9$) with typically organized verbal fluency or productive language functions; $t_{(17.4)} = -0.67$, $P = 0.511$ (2-tailed; equal variances not assumed).

Analyses and Classifications of Individuals in the Group with Atypical Lateralization

As localization of language-related activity within the brain is highly variable (Ojemann et al., 1989), there are many ways in which a particular pattern of neural activity, or lack of thereof, could be classified. Moreover, neuropsychological taxonomies can be confounded, among others factors, by the syndrome drift (Kertesz and McCabe, 1977) or the influence of the subcortical lesion component (Alexander et al., 1987). Furthermore, neuroimaging methods are highly dependable on the particular threshold used in the study (Seghier, 2008).

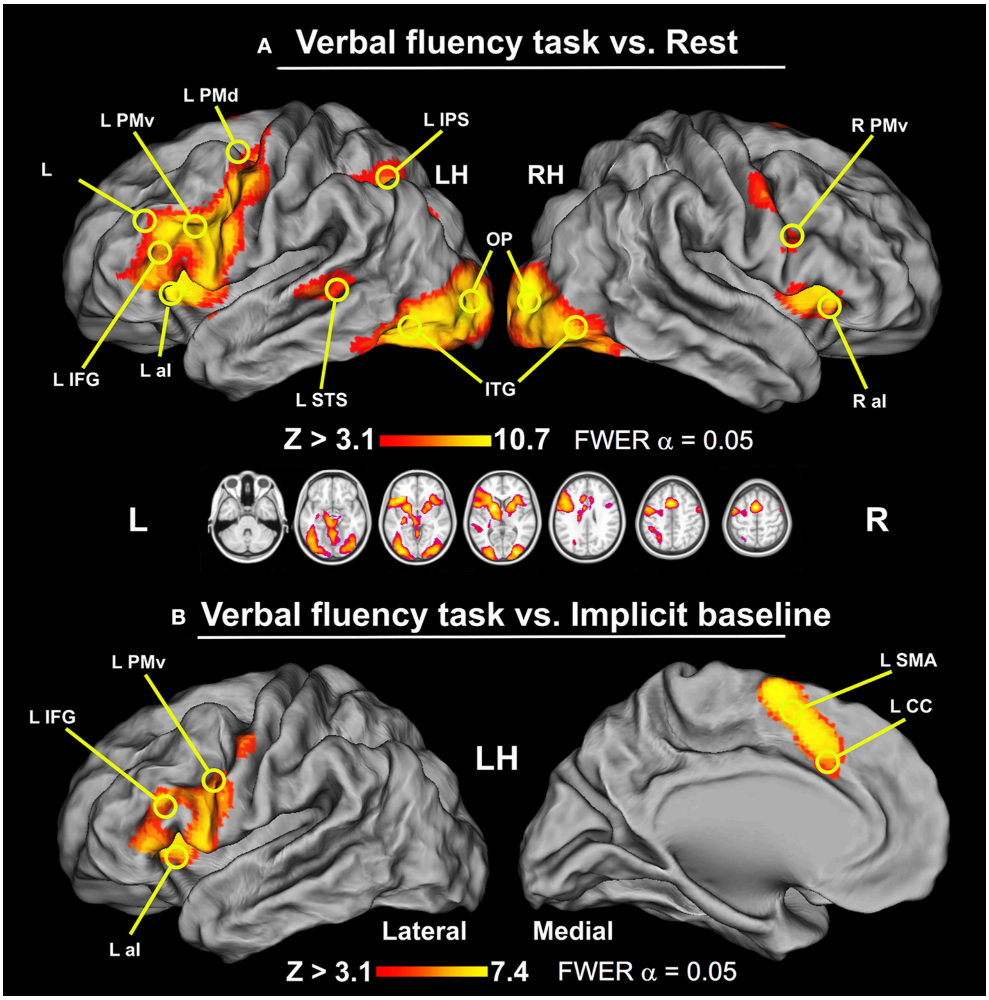

FIGURE 1 | The results of whole-brain analyses for the verbal fluency task displayed on the human Population-Average, Landmark-, and Surface-based (PALS) brain atlas (Van Essen, 2005). **(A)** Verbal fluency vs. resting baseline. This contrast revealed widespread activity involving IFG, PMd, IPS, and STS exclusively in the left hemisphere, and bilateral aI, PMv, preCG, SMA complex, mCC, ITG, FG, MOG, and OP (thresholded at $Z > 3.1$, $p = 0.05$ and cluster corrected, with critical cluster size > 177 voxels). **(B)** Verbal fluency vs. implicit baseline. Two clusters of significant signal modulations were found in the left IFG and SMA complex/mCC (thresholded at $Z > 3.1$, $p = 0.05$ and cluster corrected, with critical cluster size > 182 voxels). LH, left hemisphere; RH, right hemisphere.

Therefore, as there is no "golden standard," we tested our initial classification of the study participants using several complementary methods.

Neuropsychological investigations indicate that there are at least two populations of patients with atypical laterality of language (Basso et al., 1985; Alexander et al., 1989; Marien et al., 2004). The first one seems to be a mirror image of the typical representation, i.e., intrahemispheric organization of language is similar in atypical and typical group. On the other hand, the second group demonstrates atypical laterality and anomalous localization of language functions.

In our sample, all atypical individuals did engage classical language centers, i.e., Broca's and Wernicke's areas (WA) in the left and/or right hemisphere. As excepted, activity within the Broca's area was centered mainly in the posterior parts of IFG. In sharp contrast, neural activity within WA was more heterogeneous. Indeed, sometimes it exclusively engaged the superior temporal sulcus or superior temporal gyrus, but could be a mixture of activity within both of these structures. Nevertheless, none of our atypical individuals demonstrated anomalous localization of language functions, as shown in **Figure 3**, with the mean activity pattern displayed in the top panel on the left. Yet, due to greater variability in the localization and/or engagement of WA, this area was not revealed in the average pattern obtained for atypical representation of language.

Recently, a large neuroimaging study proposed a more refined classification of the atypical subpopulation (Berl et al., 2014). According to this report there is a three-level hierarchy of typical and atypical language patterns depending on the side, and engagement of the particular classical language areas. At the most detailed level there are 15 proposed subdivisions of individuals.

TABLE 1 | Areas of significant signal modulations.

Brain areas	MNI coordinates			*Z*-max	Cluster size (voxels)
	x	***y***	***z***		
(A) Word generation vs. rest ($Z > 8$, $P = 0.05$, clusterwise corrected for multiple comparisons, reported cluster size > 100 voxels)					
LH Putamen	−18	2	10	10.3	700
LH Supplementary Motor Area	0	2	62	10.7	513
LH Lateral Occipital Cortex	−34	−90	−4	9.6	369
LH Anterior Insula	−32	26	0	10.3	339
RH Cerebellum	32	−62	−24	10.6	313
RH Lateral Occipital Cortex	30	−92	8	10.0	288
LH Inferior Frontal Gyrus	−46	18	24	8.92	242
RH Anterior Limb of Internal Capsule	20	6	14	8.83	116
(B) Word generation vs. implicit baseline ($Z > 3.1$, $P = 0.05$, clusterwise corrected for multiple comparisons, critical cluster size > 182 voxels)					
LH Insula/Inferior Frontal Gyrus	−32	24	2	6.28	3,075
LH Supplementary Motor Cortex	−4	0	64	7.49	907

LH, left hemisphere; RH, right hemisphere.

In our sample, we found that one participant clearly exhibited right hemispheric dominance with neural activity localized in the right IFG and right WA. Other individuals demonstrated less obvious patterns, with predominantly symmetrical organization, mainly with bilateral IFG and WA engagement. Nevertheless, 91% of atypical participants had peaks of their verbal activities within the Broca's area in their right hemispheres. This right-hemisphere preponderance in this group was also clearly seen in the mean activity of the sample and this activity was limited only to right IFG. Although the reasons for the lack of involvement of WA are not entirely clear, high variability in the localization of this area, among other factors mentioned above, most likely prevented us from detecting the contribution from this language center at the group level.

Finally, we also used a novel threshold-free classification method of pattern similarity, which divided all our participants into two groups (Blondel et al., 2008). As shown in **Figure 4**, the same individuals that we grouped as atypical based on the laterality measurements were also clustered together when based on significant similarity of spatial patterns of voxels engaged within the Broca's area. All in all, voxel count LI assessment, anatomical localization of activations, verification of activity peaks, and pattern similarity support our classification of the study participants into two discrete groups—typical and atypical.

Structural Analyses of Participants' Brains

Having the participants classified to the typical and atypical groups we formally checked whether or not there are abnormal structural differences between the studied populations. First, given a report that verbal intelligence is related to the brain volume (Witelson et al., 2006) we tested if the groups differ with regards to this variable. We found no evidence of such a difference in the brain volume ($P = 0.43$). Next, we investigated the overall cortical shape of both groups. The cortical atlases of the average typical vs. atypical participants exhibited a similar shape and similar apparent left and right asymmetries reported by other groups (Van Essen, 2005; Van Essen et al., 2012). Finally, as the caudate nucleus is thought to be a marker of structural brain abnormalities related to language (Watkins et al., 2002), we analyzed its volume in atypical and typical group and found no significant differences ($P = 0.70$ for left caudate, and $P = 0.54$ for the right counterpart).

Overall, we found no significant differences between our atypical sample and typical laterality group related to the structure of the brain. This conclusion does not preclude that there are brain structural markers related to the language lateralization. It rather means that the cortical structures of both groups are free of any apparent abnormalities that are typically related to language processing.

Demographic Differences between Typical and Atypical Groups

We tested also if the studied groups differ in term of age and sex as these variables are thought to be related to language lateralization. We found no differences with regards to age ($P = 0.30$), or sex ($P = 0.78$).

Common Activity and Its Pattern for the Typical and Atypical Group

To compare the neuronal activity of a group with typical language representation and our sample with atypical language lateralization we first examined the similarity of their responses. A conjunction test with minimum statistics (Nichols et al., 2005), between the mean activity of the typical group and mean activity of the atypical sample, showed that both groups exhibited activations in aI, MOG, FG, SMA, and OP on the right during the verbal fluency task. At the subcortical level the common signal increases included primarily the right putamen, caudate, and thalamus. These results are depicted in **Figure 5A**, and can be interpreted as areas common to both groups regardless of the hemispheric dominance.

When the mean activation map of the sample with atypical language lateralization was flipped across the *x*-axis it was highly similar to the pattern of activity observed in typical individuals ($r = 0.58$). To further test this similarity, with the mean activity of the atypical sample flipped across the *x*-axis, we used the same conjunction test as before (Note, again, that this time the conjunction involved the flipped mean activity of the atypical sample and the regular mean activity of the typical group). This test showed that both groups engage similar areas, such as IFG and PMv, during the verbal fluency task. These areas were common to both groups, yet, of course, depend on the hemispheric laterality. Thus, it is critical to remember that they were activated in a mirror like fashion.

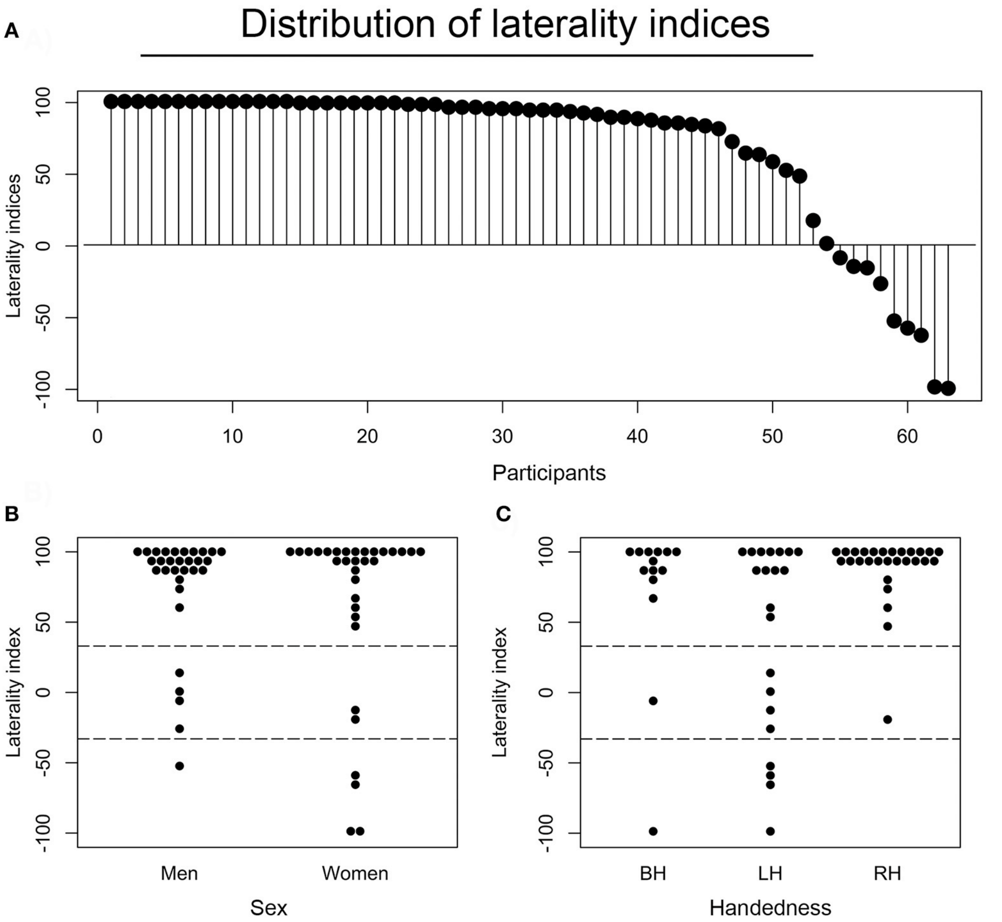

FIGURE 2 | Distributions and associations of laterality indices. **(A)** Laterality indices (LIs) for each of the participants as assessed in the Broca's area (BA44/45), and presented in the descending order. Each dot represents one individual. **(B)** A distribution of LIs across sex. **(C)** A distribution of laterality indices across handedness. BH stands for both-handed (ambidextrous), LH for left-handed, and RH for right-handed individuals.

Comparison of Typical and Atypical Group during Verbal Fluency Test

Here, we searched for group differences in the voxelwise (whole brain) analysis of neuronal activity during our version of the verbal fluency task. Such a test examines not only differences in active regions but also signal modulations in previously undetected areas.

Typical Group > Atypical Group

The participants with typical representation of language showed significantly greater signal modulations within an inferior frontal cluster located in the left hemisphere. Specifically, the observed differences with the atypical group encompass the left inferior frontal gyrus through frontal operculum. This effect is shown in **Figure 5B** on the left.

Atypical Group > Typical Group

The participants with atypical language laterality exhibited, in turn, significantly greater signal modulations in the right hemisphere, mainly in the frontal, parietal and temporal lobes. More specifically, the observed differences with the typical group encompass significant signal alterations detected in the superior frontal sulcus (SFS), MFG, IFG, PMv, and SMA. In the temporal lobe, the analysis revealed that the caudal middle temporal gyrus (cMFG) was also differentially engaged between both groups. Likewise, we found similar modulations along the IPS, and ANG. These results are depicted in **Figure 5B** on the right.

Comparison of the Extent of Activity between the Typical and Atypical Group during Verbal Fluency Test

Both conjunction and correlation analyses revealed that the studied participants exhibited highly similar patterns of neural responses during our verbal fluency test. However, it is still possible that the atypical language representation is more diffuse than typical organization of this function. To investigate this possibility, we first compared the relationships between the laterality indices obtained in the Broca's area and the overall number of activated voxels across the whole hemisphere. An unpaired *t*-test revealed that our sample with atypical laterality

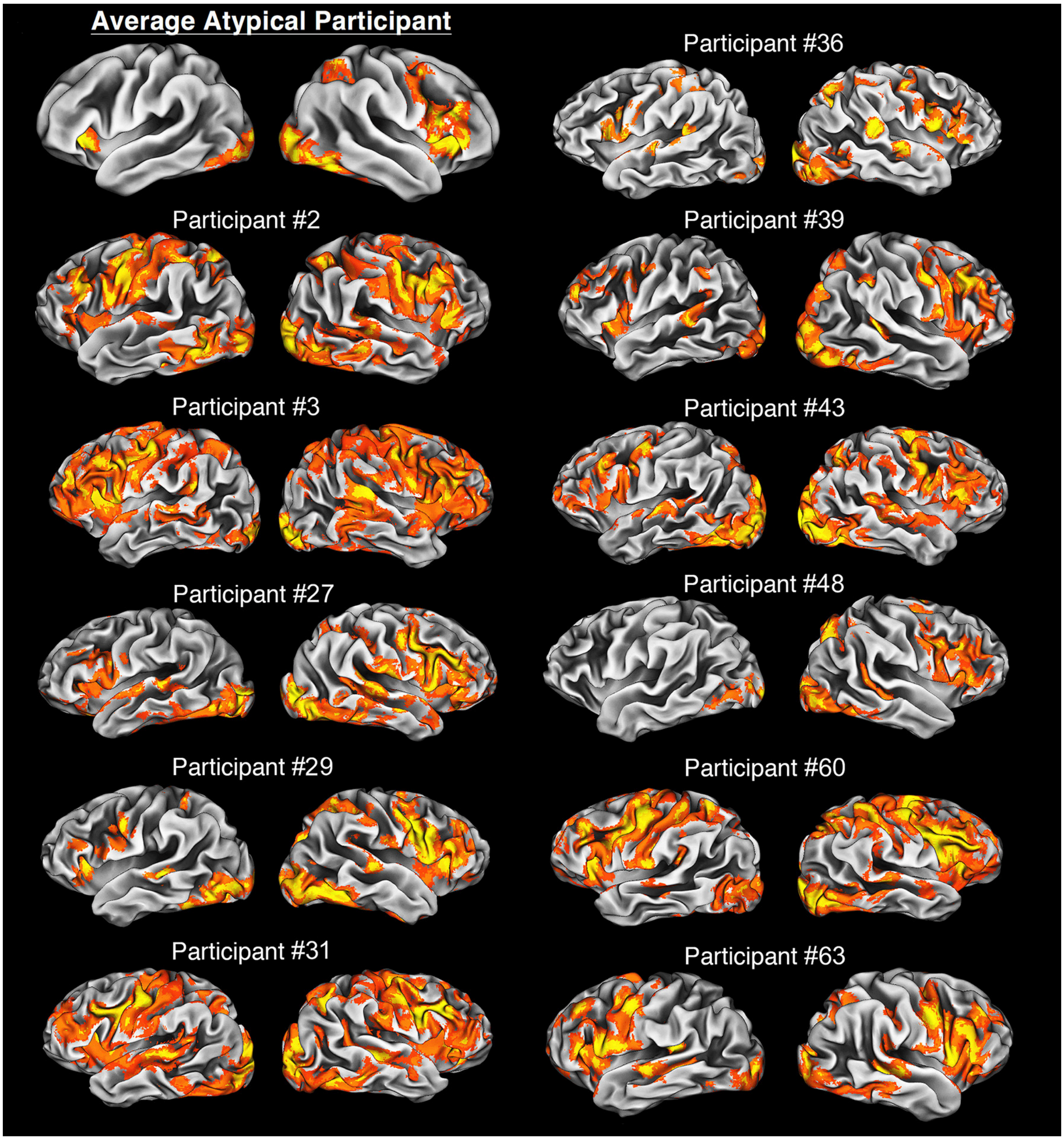

FIGURE 3 | Average and individual neural activity in participants with atypical lateralization of language revealed during our verbal fluency task vs. rest. The average neural activity is overlaid on the average cortical representation of the whole atypical sample, and in all other cases, individual activity patterns are projected on individual cortical representations. All images were thresholded at $Z > 2.3$, $p = 0.05$, with clusterwise correction for multiple comparisons, and a critical cluster size adjusted for each individual. Notably, participants with the bilateral organization of language have a clear tendency to use more cortical tissue during this task, e.g., participants #2 and #3. In sharp contrast, an individual (#48) with strong right hemispheric dominance has quite focused language representation. Finally, it is of note that in general the atypical group exhibits clear right hemispheric dominance.

had a clear tendency to use more cortical tissue (as measured with the number voxels involved) for the control of language than our group with typically represented language [$t_{(11.35)} = -2.07$; $P = 0.06$]. There was, however, a much more interesting and significant relationship between the absolute values of laterality indices (irrespective of their direction) and the number of voxels used regardless of handedness ($r_{61} = -0.61$, $P \ll 0.001$). The lower the laterality index (the more bilateral the activity), the more cortical tissue was involved across the whole hemisphere in the control of language. This negative correlation is depicted in **Figure 6**.

Peaks of Activity within Broca's Area

We found a statistically significant difference between locations of peaks in the z-axis in typical and atypical group ($P = 0.046$). Specifically, atypical group had their peaks of activity located

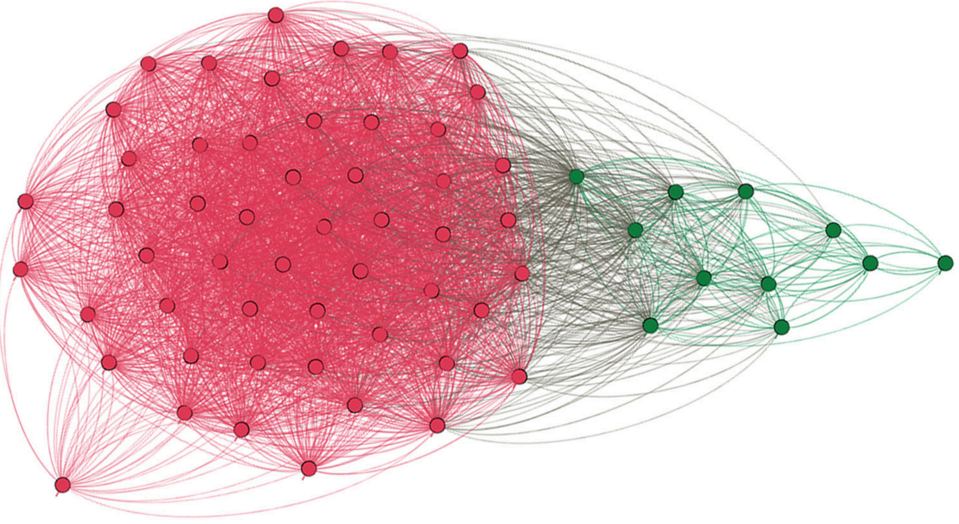

FIGURE 4 | Graph depicting similarity between language patterns in the studied individuals. Each dot denotes a particular participant, each line represents similarity between language patterns as measured in the unthresholded Z-stat image within the Broca's area. Modular algorithm was used to find subgroups within all tested individuals, and the result is clear cut—two distinct groups which are depicted with different colors. Namely, magenta red represents typical participants, whereas dark green individuals with atypical laterality of language. Importantly, the number of groups and their members were exactly the same as the ones obtained using LI assessment which was based on the thresholded voxel count.

lower (mean $z = 16$) than typical group (mean $z = 22$). Counter to the previous reports of differences in the location of peaks along the y-axis (Voets et al., 2006), with atypical participants having their peaks located more posteriorly, we did not observe a significant difference along this dimension. (Although this analysis was performed on the peaks from the initial exploratory examination with traditional threshold of $Z > 2.3$, the location of peak activity should not be threshold dependent).

A Comparison of Typical and Atypical Group during Resting-State Scans

The peak-activated voxels from the clusters enlisted in **Table 2** (and found in the previous group comparisons) were used as seeds for the connectivity analyses. While virtually no differences in connectivity patterns were detected, this analysis revealed that the left-hemisphere cerebellar seed exhibited significantly stronger connectivity with the right OP in the typically lateralized group. These results are presented in **Figure 7**.

Comparison of the Resting-State Global Signal between Typical and Atypical Group

Given a recent report (McAvoy et al., 2016) which suggests that lateralization is also reflected at the level of the brain's global signal, i.e., mean signal across the whole brain during a resting-state scan, we also examined whether or not there are asymmetries in the hemispheric global signal distribution between the studied groups. As anticipated, the global signal from the left hemisphere, contrasted with the right-hemisphere signal, in typical group was greater in the ANG, precuneus (pC), SFG, and left caudal MFG. Using the network atlas available (Yeo et al., 2011), in the fsaverage template we were able to identify the above mentioned regions as a part of the DMN. In contrast, the right hemisphere signal, when compared to the left hemisphere signal, was greater in the typical group in the supramarginal gyrus (SMG), aI, aMFG, and right cuneus. These regions, when compared with the fsaverage network template, were shown to be a part of the ventral attention network. The opposite pattern, i.e., right hemisphere signal dominance in the ANG, pC, SFG, and left caudal MFG; and greater left hemisphere signal in SMG, aI, aMFG have been observed for our sample with atypical language laterality. The results of the comparisons between the typical and atypical group are displayed in **Figure 8**.

DISCUSSION

This study investigated the neural underpinnings of atypical lateralization of language in healthy individuals and examined the idea that atypical laterality is a mirror image of the left hemispheric language dominance. We found that both studied groups used similar brain structures in a mirror fashion during our verbal fluency task. However, atypical sample also engaged the right hemispheric DMN components. Moreover, we found that atypical organization of language entails more diffuse processing and/or mechanism. Finally, we detected alterations in the resting-state intrinsic connectivity at the local and global level. These findings shed a new light on our understanding of the hemispheric differences in the organization of language in three key ways.

First, we have found that atypical laterality is associated with substantially greater engagement of frontal and temporal structures in the right hemisphere. Such differences cannot

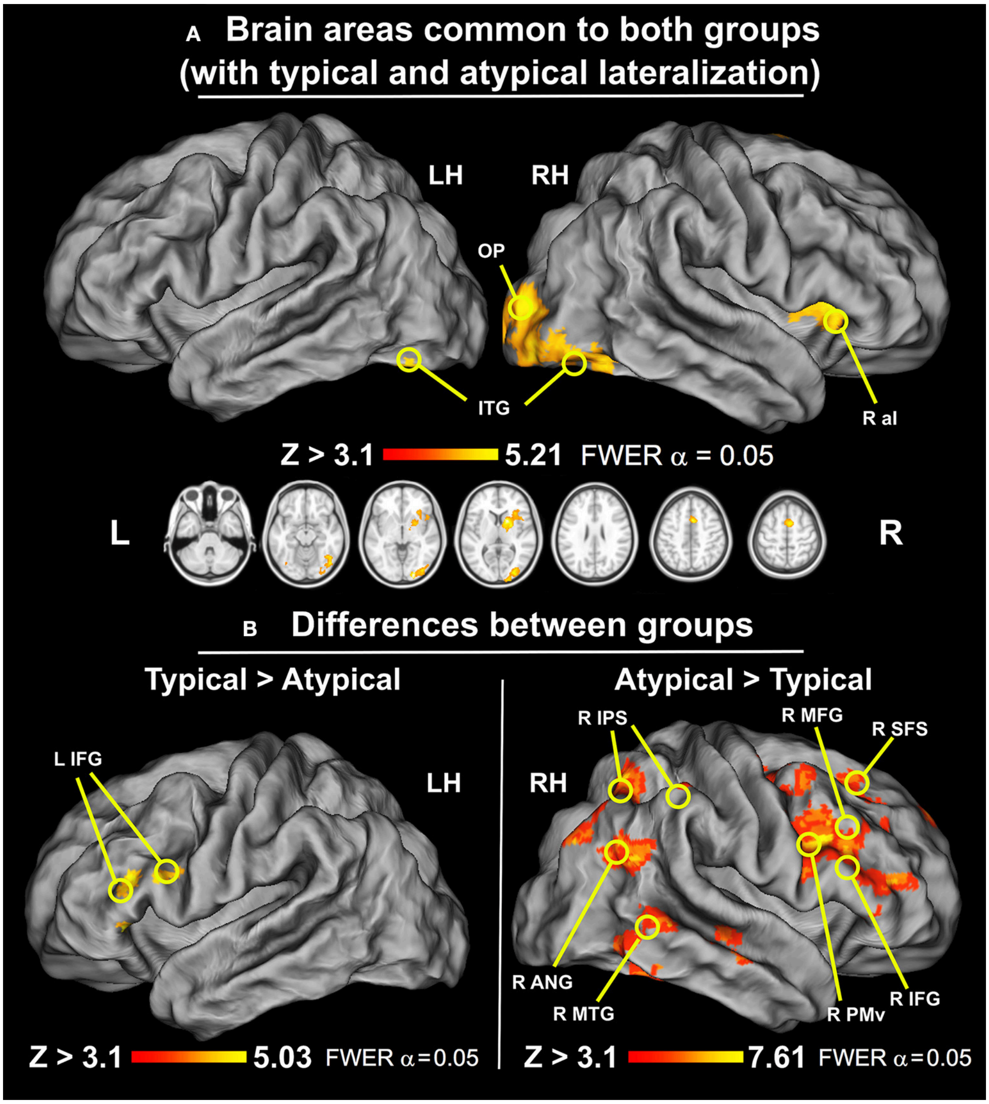

FIGURE 5 | Similarities and differences between groups with typical and atypical language lateralization (thresholded at $Z > 3.1$, $p = 0.050$ cluster corrected; critical cluster size > 179 voxels). **(A)** Common regions for typical and atypical language lateralization. Both groups used right aI, MOG, FG, OP, caudate, and putamen during performance of the verbal fluency task. **(B)** Regions involved more in either typical or atypical language lateralization. Left: A direct group comparison of individuals with typical and atypical neural activity during silent word generation. Significant signal modulations were located only along the left IFG. Right: A direct group comparison of participants with atypical and typical language laterality during silent word generation. Significant modulations of neural activity were observed in right SFS, MFG, IFG, PMv, SMA, cSTG/cMTG/cITG, IPS, and ANG.

be explained in terms of mirrored representation because individuals with typical lateralization did not show a reversed pattern. Thus, atypical representation of language entails qualitative differences in its general organization. Second, although we have demonstrated that both groups exhibited highly similar overall pattern of functional activity, a more diffuse—i.e., wider in its extent—representation of language was clearly associated with its bilateral organization. Thus, atypical laterality also entails sharp quantitative differences in the representation of language skills. Third, we have shown that the connectivity patterns of the cerebellum get altered—are substantially weaker—in the atypical language representation. Finally, there are also clear differences between the two groups in the spontaneous activity/connectivity patterns revealed by the distribution of the hemispheric global signal from resting-state scans. These effects were particularly pronounced in the ventral attention and DMNs in the atypical, as compared to typical, language laterality. The unique quantitative and qualitative differences in neural processing, associated in this study with atypical lateralization of language at several levels of analysis, provide strong and convincing pieces of evidence that atypical lateralization is not a simple mirror image of the typical left hemispheric language specialization.

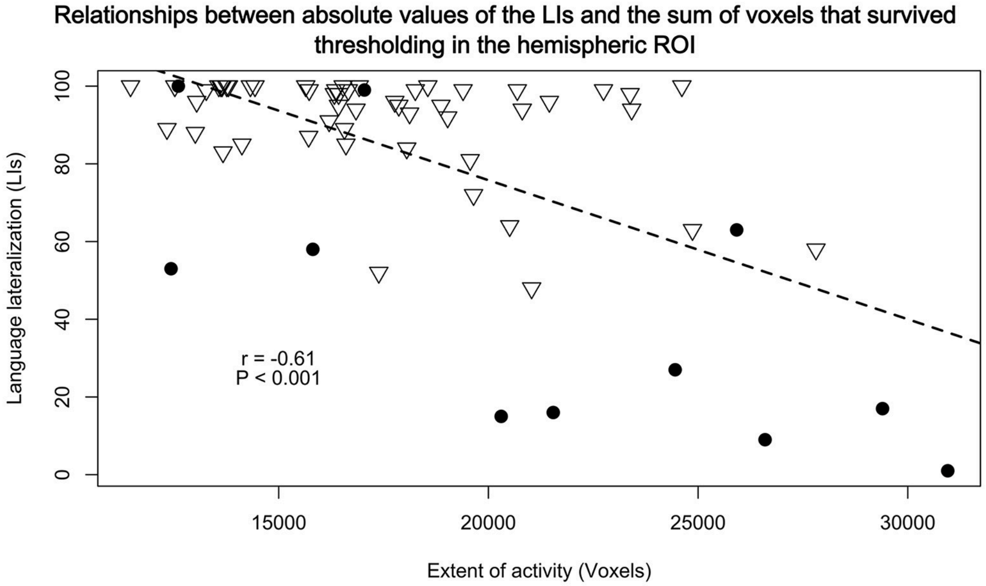

FIGURE 6 | Relationships between absolute values of the LIs from BA 44/45 and the sum of voxels that survived thresholding, calculated in a similar manner as with the BA's LIs, in the hemispheric ROI. There were significant negative correlations ($r_{61} = -0.61$, $P < 0.001$) such that the less lateralized the brain activity the greater extent of language representation. Triangles represent participants with typical lateralization of language, and dots with atypical language lateralization.

TABLE 2 | Areas of significant group differences from initial exploratory analyses ($Z > 2.3$, $P = 0.05$, clusterwise corrected for multiple comparisons, critical cluster size > 667 voxels).

Brain areas	MNI coordinates			*Z*-max	Cluster size (voxels)
	x	*y*	*z*		
(A) Typical group > Atypical group					
LH Inferior Frontal Gyrus	−42	30	0	3.64	689
(B) Atypical group > Typical group					
RH Middle Frontal Gyrus	40	16	26	4.51	6,772
RH Intraparietal Sulcus	34	−58	52	3.99	3,305
RH Inferior Temporal Gyrus	52	−46	−18	3.88	2,687
LH Cerebellum	−24	−86	−22	3.9	1,289

RH, right hemisphere; LH, left hemisphere.

Atypical Lateralization of Language: Abnormality?

It has been suggested for a long time that atypical lateralization of language results from an early brain injury. Nonetheless, we have found bilateral or right hemispheric language representation in 17% of 63 healthy participants examined in the present study. It should be emphasized that none of these individuals had any sign of structural brain abnormalities or any obvious language impairment, which could cause or be linked to atypical laterality. Specifically, overall brain volumes, cortical shapes, and the sizes of the caudate nuclei, with the latter (when smaller) being considered critical markers of language impairments in the brain (Watkins et al., 2002), did not differ between groups. These observations are consistent with the outcomes from previous reports in which language laterality was investigated in a large group of healthy (*normal*) non-right-handers (e.g., Pujol et al., 1999; Knecht et al., 2000b; Szaflarski et al., 2002). In short, our results cannot be easily linked to any anatomical or functional abnormality, and most likely reflect a natural variation in the hemispheric specialization for language, which is usually underestimated (Kroliczak et al., 2011). The obtained outcomes are consistent with an earlier report which demonstrated that atypical language lateralization, which is a part of this continuum, is not related to impairments in intelligence, verbal fluency, or academic achievements (Knecht et al., 2001). Moreover, our study shows that this type of functional specialization is associated with quite specific neural characteristics, and connectivity profiles. Thus, both language systems yield similar behavioral outputs despite substantially different neural underpinnings. Below, we further discuss differences and similarities between the studied groups, both in terms of the disparate profiles of neural activity, and resting-state connectivity.

Atypical Lateralization of Language: Different or Similar Pattern of Activity?

In general, when flipped across the x-axis, both of the studied groups exhibited highly similar pattern of activity during a verbal fluency task, yet with some notable differences. The commonalities and disparities between the sample with atypical language lateralization and our group of participants with typical language organization appear to correspond well to the two cerebral systems that could be engaged in the planning and

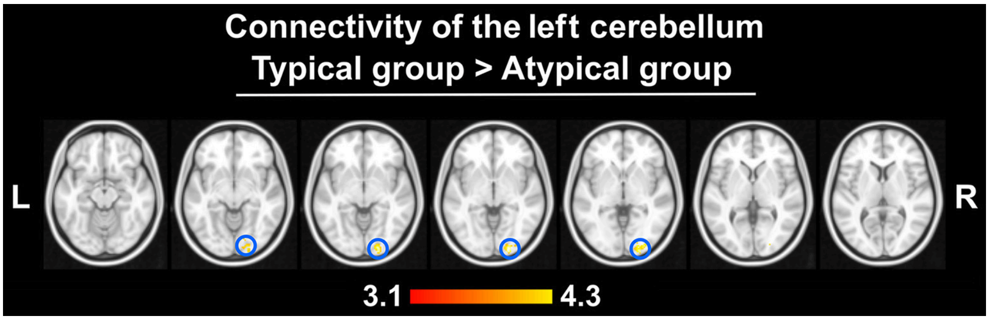

FIGURE 7 | Differences in connectivity between groups (thresholded at $Z > 3.1$, $p = 0.050$ cluster corrected; critical cluster size > 69 voxels). The left cerebellum seed displayed stronger connectivity only with the right OP in the typical group. No other seeds yielded significant results.

execution of motor programs (Leiguarda and Marsden, 2000). The basal ganglia, and SMA, represent the system for overlearned skills (Grafton et al., 1995), with areas common for both groups and hemispheres. In sharp contrast, although IFG and PMv engagement is also common for both groups, it, nevertheless, clearly depends on hemispheric laterality. These two regions belong to the second system which is pronounced during the planning/execution phases of movement (Kroliczak et al., 2011; Vingerhoets et al., 2012), a system which has been also shown to mediate less rehearsed tasks (e.g., Kroliczak et al., 2007). This network is engaged noticeably more in the sample with atypical laterality as it includes also the right parietal and temporal cortices. In the group with typically organized language the processing is narrower and, at least for language tasks, is limited to greater signal modulation in the left IFG. This latter region, together with MFG and SMG, belongs to the praxis planning network (Johnson-Frey et al., 2005; Kroliczak et al., 2008; Przybylski and Kroliczak, 2017) characteristically engaged in typical populations and tasks (see also Marangon et al., 2016), and whose subdivisions are also typically invoked during action imitation (Kubiak and Kroliczak, 2016).

The substantial engagement of both the above-mentioned neuromotor mechanisms in a verbal fluency task is not that surprising. Indeed, recent evidence suggests the existence of a close link between the lateralization of language and praxis (Kroliczak et al., 2011; Vingerhoets et al., 2013; Goldenberg and Randerath, 2015; see also Kroliczak et al., 2016; Corballis, 2017). Specifically, individuals with atypical organization of language demonstrate also atypical representation of skilled movements (praxis). Here, we showed that atypical language laterality is related to widespread changes in the network potentially specialized for both language and praxis.

Importantly, in the sample with atypical laterality there were also differences in signal modulations that could not be explained by a mirror reversal of the left hemisphere activity. Specifically, the *atypical* sample engaged more the right ANG, middle part of the MTG, and SFG during the silent word generation task. These regions belong to the DMN (Greicius et al., 2003), which encompasses a large part of the frontal, temporal, and parietal cortices (Raichle, 2015). DMN is thought to support internal mentalization related to our plans for future, autobiographical memory recall, and other spontaneous thoughts not related to the task (Buckner et al., 2008). As this network is more active during rest (Binder et al., 1999), we did not observe its engagement in the contrast of our language task vs. resting baseline. Although there is no consensus among research concerning DMN detailed anatomy (see differences in the early formulation of the concept: Shulman et al., 1997; Binder et al., 1999; Mazoyer et al., 2001; Raichle et al., 2001), and possible existence of sub-networks (Sestieri et al., 2011; Braga and Buckner, 2017), the core elements of this system are ANG, posterior cingulate cortex, MTG, and SFG. Importantly, in two of the structures just mentioned, i.e., the ANG and MTG, neural activity was significantly greater in the right hemispheres of participants from the atypical group. In sharp contrast, in the typical group, the left ANG and MTG did not seem to be involved. As DMN is thought to be engaged in semantic processes (Binder et al., 2009), which are closely tied to language, some possible effects of language laterality on this network could not be excluded. Therefore, this result opens an exciting possibility of differences in the organization of this prominent brain network that are related to the lateralization of language. Indeed, these outcomes are also interesting in light of recent findings (Doucet et al., 2014) suggesting that the temporal lobe epilepsy, which could cause atypical laterality, alters the frontal parts of the DMN. Yet, our results clearly demonstrate that atypical language laterality in healthy individuals is related to a greater engagement of the two key posterior components of the DMN. This difference should then be of great clinical importance.

Overall, the widespread changes in the neural patterns of activity associated with atypical language lateralization involve substantial part of the classically-defined motor/praxis planning network in a "mirror fashion" to those with typical laterality. Arguably, there is also a much more important, and much greater engagement of the right hemispheric default mode components.

Atypical Lateralization of Language: Diffused or Focused Representation?

The nature of the hemispheric language representation is an important element of any theory of the lateralization of brain functions (Bishop, 2013). Some of these theories

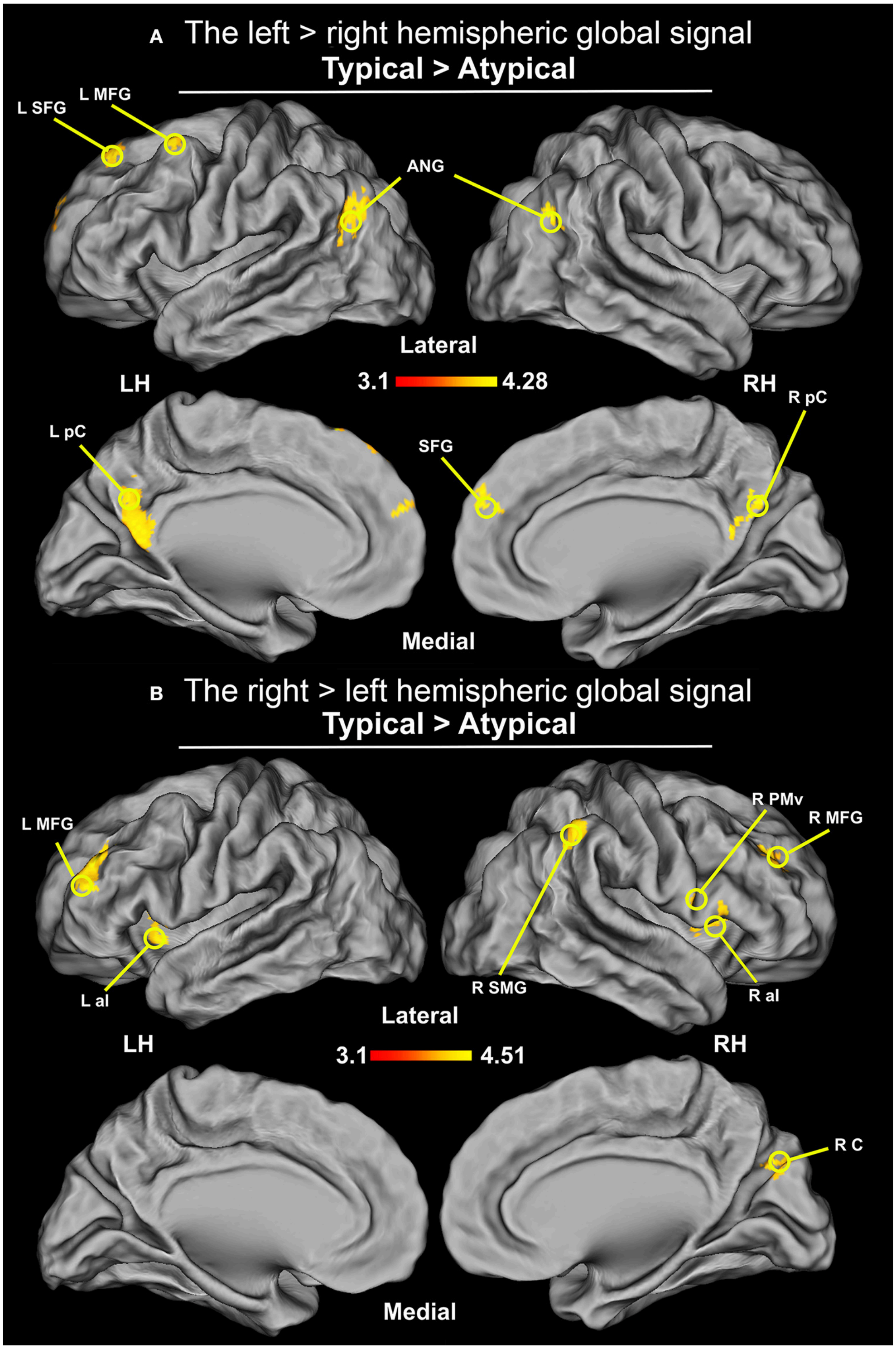

FIGURE 8 | Differences in the distribution of the hemispheric global signal between groups (thresholded at $Z > 3.1$, $p = 0.05$ cluster corrected; critical cluster size > 71 voxels). The signals come from the initial multiple regression performed without any seed. **(A)** Distribution of global signal from the between-groups comparison of the left hemisphere contrasted with the right hemisphere. Increased connectivity was observed in ANG, pC, and SFG, as well as MFG for the group with typical language laterality. **(B)** Distribution of global signal from the between-groups comparison of the right hemisphere contrasted with the left hemisphere. Increased connectivity was observed in SMG, PMv, and cuneus (RC)/parieto-occipital sulcus, as well as in aI, and rostral division of MFG for the typical language laterality group.

suggest that atypical language organization would entail a diffuse functional network (Brown and Hecaen, 1976). Our results partially corroborate this hypothesis, yet with an important caveat. We found that there is a strong negative relationship between the amount of cortical tissue used during the verbal fluency task and the absolute degree of lateralization. Specifically, only individuals with bilateral language representation demonstrated a more diffuse functional organization. Note that this relationship is non-trivial in the sense that different number of voxels (representing the extent of cortical tissue used) can give similar LIs (Seghier, 2008). In other words, bilateral language organization, represented with low LI scores, could be demonstrated by two small/focused clusters of highly symmetrical activity in BA 44/45, or a much more diffused—i.e., large in terms of spatial extent, even if with less symmetrical localization of foci of—activity in this ROI. Importantly, our analyses revealed that subjects with complete right hemisphere language lateralization demonstrate focused activation as individuals with typical laterality. As such, this outcome is similar to the result obtained in an earlier study (Knecht et al., 2003), which compared subjects with right hemisphere language lateralization with matched typical individuals. In the context of all these findings, it seems that there is a continuum of representations ranging from diffuse language network characterized by small absolute values of LIs, to more focal functional organization (either left or right lateralized) characterized by greater absolute values of LIs. These results fit well with an earlier proposal (Price and Crinion, 2005) that the dominant hemisphere for language inhibits the activity of the non-dominant one. Individuals with bilateral representation of language could lack of or have substantially smaller inhibitory influence of this kind. This could, in turn, result in a more diffuse language organization, as measured with the spatial extent.

The above-mentioned findings, based on voxel counting, may still require a dose of healthy skepticism. After all, some studies suggest that this method is suboptimal and has inherent drawbacks (Poldrack, 2007). Nevertheless, in the realm of language research, voxel counting is a reliable method which ensures sensitivity and specificity, even when compared to the Wada test, which is a standard in clinical practice (Dym et al., 2011).

Peaks of Activity: An Interesting Direction for Future Studies

The locations of peaks of activity within the Broca's area in both groups were different along the z-axis, with the one for the atypical group located lower. With this in mind, using the Neurosynth tool (www.neurosynth.org), we performed initial exploration of the connectivity differences that could be related to this result. Interestingly, we found that the mean peak of the typical group ($x = -52$, $y = 14$, $z = 22$) is widely connected with the WA and SMG, i.e., typical posterior language areas. In sharp contrast, the mean peak for the atypical group ($x = 52$, $y = 14$, $z = 16$) had only limited connectivity with the temporal lobe, and in the parietal lobe it was connected to the postcentral sulcus instead of SMG. Although, we are aware of the limitations related to the above results, we nevertheless point out that future studies should seriously consider such differences in connectivity patterns.

Three possible caveats related to these findings involve: substantial anatomical variability of the Broca's area (Keller et al., 2007), even small registration errors, as well as using a large smoothing kernel (here: of 6.2 mm). Indeed, it has been demonstrated that spatial smoothing can shift peaks of activity in the fMRI results (Jo et al., 2008). Nevertheless, we are convinced that the functional difference observed in this study between typical and atypical group could be of great scientific interest, particularly in the light of the above-mentioned alterations in connectivity. Indeed, studies using surface-based methods of registration and smoothing could easily validate our conclusions.

Language Laterality and Handedness

An association between handedness and language laterality has been postulated almost from the very beginning of investigations on language representations in the brain. However, no clear relationships between these variables have been found (see Haberling and Corballis, 2015). Indeed, recent outcomes suggest that although there is some anatomical overlap between networks contributing to hand preference (handedness) and language laterality (i.e., right PMv) there is little functional overlap. Specifically, handedness can affect language laterality only indirectly, e.g., by influencing the praxis network (Gainotti, 2015; Haberling and Corballis, 2015; Badzakova-Trajkov et al., 2016), which is in turn more closely related to language (Corballis, 2003; Kroliczak et al., 2011, 2016; Vingerhoets et al., 2013). These results correspond well with recent studies suggesting that handedness and language lateralization are related only indirectly, but left-handedness increases the likelihood of bilateral or right-hemispheric language specialization (Somers et al., 2015; Joliot et al., 2016). Therefore, a right-handed individual with left hemisphere dominance would exhibit a similar functional organization as a left-hander with the left hemispheric specialization. Indeed, when we compared left-handers with right-handers and controlled for LIs no significant differences between these groups were found.

Local Resting-State Connectivity Differences

We found that the connectivity of cerebellum differs between the studied groups. Specifically, we showed that the left cerebellum in the group with typical language organization exhibited greater connectivity with the right early visual cortex. This result is consistent with recent observations that the cerebellum also plays a critical role in language processing (e.g., Booth et al., 2007), and language-related experience itself can influence the functioning of cortical networks for vision (Dehaene et al., 2010; Szwed et al., 2012; see also Siuda-Krzywicka et al., 2016). Yet, other studies which examined connectivity of the cerebellum did not find a link between these structures (Buckner et al., 2011). However, most of them used global signal regression that potentially alters the intrinsic connectivity. Although, the exact functional importance of the link between the cerebellum and early visual cortices can be debated, our results clearly show that this pattern of connectivity is influenced by language lateralization.

Global Resting-State Connectivity Differences

Somewhat surprisingly, the most robust results were found when we examined differences in the hemispheric resting-state global signals between groups (i.e., at a global but not local connectivity level). Specifically, both groups differ in the connectivity of the ventral attention and DMNs. Recently, hemispheric global signal from the left hemisphere has been mapped onto language related areas, whereas right hemispheric global signal has been linked to the attention network (McAvoy et al., 2016). Our results corroborate these findings, at the same time substantially extending their interpretation. Specifically, we have demonstrated that atypical language laterality can alter even the hemispheric global signal during resting-state. These results correspond well with the outcomes from a recent study which showed that there is a complementary hemispheric specialization for language and visuospatial attention (Cai et al., 2013). In fact, as our results suggest, this complementary specialization is also reflected in the hemispheric global signal. Moreover, we found that the asymmetry of hemispheric global signal at rest affects the laterality of the DMN. This finding parallels well with the outcomes from our language task, which showed that atypical individuals utilized more the right hemisphere DMN components during silent word generation.

Clinical Importance

Our results indicate that a transfer of language functions from one hemisphere to another is associated with widespread alterations in connectivity and often a more diffuse representation of language itself. This complex process could be influenced by a variety of variables, e.g., the age at which an epileptic episode occurs in the left hemisphere, the extent of a lesion, structural asymmetries of unknown etiology, etc., and, therefore, could result in diverse outcomes. Indeed, recent studies (Liegeois et al., 2004; Raja Beharelle et al., 2010) suggested that in some cases the right hemisphere may not be capable of sub-serving language functions in the face of an early left brain injury. Therefore, our results showing alterations related to the atypical language laterality in a healthy brain are of vital importance for the clinical practice by showing changes that possibly must occur in the injured brain to fully accommodate language functions. Indeed, a recent study (Yourganov et al., 2016) showed that this approach, utilizing mainly connectivity data, could predict post-stroke language impairments.

Generalizability of the Obtained Results to Representations of Other Languages

Although native speakers of Polish (the most commonly spoken Western Slavic language) were tested in this project, the outcomes should be easily generalizable to other languages, including English. Of course, when compared to modern English, Polish has some unique features: rich inflectional morphology, grammatical gender, relatively free word order, as well as some differences in phonology to name just a few. Yet, in earlier studies from our laboratory we convincingly demonstrated that the lateralization of single word utterances and processing is quite similar in Polish and English (Krefta et al., 2015; Klichowski and Kroliczak, 2017).

CONCLUSIONS

The fact that more than one neural mechanism can give similar output seems to be still underappreciated in cognitive neurosciences. Here, we showed that atypical language lateralization is a part of a natural continuum of hemispheric specializations. This type of functional representation seems to be related to handedness, yet only in an indirect way, i.e., it has some anatomical overlap but little functional connection. If it is bilateral it then entails a more diffuse representation of language functions. Moreover, individuals with atypical language organization engage more the right DMN components during a language task. There are also important differences in neuronal responses that manifest themselves during resting-state. Specifically, right-sided and bilateral representation of language alters brain connectivity of the cerebellum, and even leads to changes in the hemispheric resting-state global signal. Importantly, these differences are not accompanied by any vivid behavioral impairment, or brain abnormality. Therefore, we conclude that atypical lateralization of language is a natural and unique variant of functional representation.

AUTHOR CONTRIBUTIONS

This project was designed by SB and GK. Data were collected by ŁP and MP, analyzed by SB, and interpreted by SB, MP, ŁP, and GK. The manuscript was written by SB and GK.

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The Functional Genetics of Handedness and Language Lateralization: Insights from Gene Ontology, Pathway and Disease Association Analyses

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Handedness and language lateralization are partially determined by genetic influences. It has been estimated that at least 40 (and potentially more) possibly interacting genes may influence the ontogenesis of hemispheric asymmetries. Recently, it has been suggested that analyzing the genetics of hemispheric asymmetries on the level of gene ontology sets, rather than at the level of individual genes, might be more informative for understanding the underlying functional cascades. Here, we performed gene ontology, pathway and disease association analyses on genes that have previously been associated with handedness and language lateralization. Significant gene ontology sets for handedness were anatomical structure development, pattern specification (especially asymmetry formation) and biological regulation. Pathway analysis highlighted the importance of the TGF-beta signaling pathway for handedness ontogenesis. Significant gene ontology sets for language lateralization were responses to different stimuli, nervous system development, transport, signaling, and biological regulation. Despite the fact that some authors assume that handedness and language lateralization share a common ontogenetic basis, gene ontology sets barely overlap between phenotypes. Compared to genes involved in handedness, which mostly contribute to structural development, genes involved in language lateralization rather contribute to activity-dependent cognitive processes. Disease association analysis revealed associations of genes involved in handedness with diseases affecting the whole body, while genes involved in language lateralization were specifically engaged in mental and neurological diseases. These findings further support the idea that handedness and language lateralization are ontogenetically independent, complex phenotypes.

Keywords: handedness, language lateralization, ontogenesis, gene ontology, asymmetry, genetics

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INTRODUCTION

Handedness and language lateralization are complex phenotypes and represent different aspects of functional brain asymmetries. Hemispheric asymmetries are a major principle of brain organization in many vertebrate (Ocklenburg et al., 2013d; Ströckens et al., 2013; Güntürkün and Ocklenburg, 2017) and invertebrate species (Frasnelli, 2013). In humans, handedness and language lateralization are related to some extent. Both are mostly controlled for by the left hemisphere in right-handed individuals. Moreover, left-handedness is associated with a higher probability for right-hemispheric language lateralization (Knecht et al., 2000; Somers et al., 2015). The predominance of the left hemisphere in processing fast temporal changes makes it ideally suited to process both complex motor function (Barber et al., 2012) and language (Slevc et al., 2011; Scott and McGettigan, 2013). This association prompted some authors to assume that one single gene determines both handedness and language lateralization: For example, the 'Right-Shift Theory' (Annett, 1975) proposes a single dominant allele (RS+), which increases the chance of being right-handed with a left-hemispheric dominance for language. The alternative recessive allele (RS−) does not influence lateralization, which reduces the 'right-shift' in RS+− individuals. In homozygous RS−− individuals, the direction of handedness and language lateralization is determined by chance. A similar single gene model has been conceived by McManus (1984, 1985), who proposed a dextral allele (D), which results in 100% right-handedness and left-hemispheric language dominance in homozygotes (DD). The chance allele (C) does not affect lateralization, so that right- and left-handedness occur with a probability of 50% each in the homozygote variant (CC). The heterozygote phenotype (DC) was proposed to result in a 75% probability of right-handedness. However, these early genetic theories are solely phenotype-driven and are not supported by molecular genetic evidence. In contrast, a number of twin studies estimated that around 25% of variance in handedness data is due to additive genetic effects. The remainder is suggested to be influenced by non-genetic factors (Medland et al., 2006, 2009; Vuoksimaa et al., 2009). In fact, no single gene has been identified as a potential exclusive determinant of handedness and language lateralization. Despite sample sizes allowing for adequate statistical power, evidence from genome-wide association studies (GWASs) strongly argues against the existence of such a gene (Eriksson et al., 2010; Ocklenburg et al., 2013c; Armour et al., 2014). However, these studies do not disprove the existence of a genetic component in handedness development *per se*. As suggested by McManus et al. (2013), a key biological model for the genetics of handedness is primary ciliary dyskinesia (PCD), which results in situs inversus, a mirror reversal of visceral organs, in 50% of all cases. Not surprisingly for a complex phenotype, at least 16 loci involved in PCD have been found so far. Similarly, molecular genetic studies suggest that multi-locus models might be a more suitable explanation for the ontogenesis of hemispheric asymmetries. Armour et al. (2014) suggest that at least 40 and potentially up to 100 genes are involved in the determination of functional lateralization.

Genes associated with handedness include *LRRTM1* (Francks et al., 2007), *PCSK6* (Scerri et al., 2011; Arning et al., 2013; Brandler et al., 2013; Robinson et al., 2016), *AR* (Medland et al., 2005; Hampson and Sankar, 2012; Arning et al., 2015), *COMT* (Savitz et al., 2007), *APOE* (Bloss et al., 2010; but see Hubacek et al., 2013; Piper et al., 2013), and *SETDB2* (Ocklenburg et al., 2015a). Genes associated with language lateralization include *FOXP2* (Pinel et al., 2012; Ocklenburg et al., 2013b), *CCKAR* (Ocklenburg et al., 2013a), *GRIN2B* (Ocklenburg et al., 2011), and others (see below). However, these genes explain only a fraction of the variance in the respective phenotype. To this date, no study could reveal an association of one gene with both language lateralization and handedness that would point towards a shared genetic basis. Therefore, Ocklenburg et al. (2014) proposed that handedness and language lateralization differ in both their neurophysiological basis and genetic correlates. The authors suggest a relationship of partial pleiotropy between both phenotypes, i.e., handedness and language lateralization have shared as well as independent ontogenetic influencing factors contributing to their development.

Uncovering the ontogenesis of hemispheric asymmetries requires deeper knowledge of genes involved in their development. However, specifically investigating individual genes gives rise to different methodological difficulties: First, genes can never be interpreted on their own, but have to be regarded in the context of other genes (Zhang et al., 2015) and environmental factors (Asor and Ben-Shachar, 2016; Gattere et al., 2016). Second, another promising way to shed light on the development of hemispheric asymmetries is comparing gene expression between the left and right hemisphere. Grouping of genes into functional sets could manifest hemispheric asymmetries that are too subtle to uncover on the level of individual genes (Karlebach and Francks, 2015). Accordingly, gene ontology (GO) sets classify genes into functional groups depending on their biological effects. Applying GO analysis on a certain list of genes reveals information on shared molecular functions of these genes, their contributions to biological processes and their corresponding cellular locations (Gene Ontology Consortium, 2015). Here, we applied GO analyses on genes previously associated with handedness on the one hand and genes previously associated with language lateralization on the other hand to identify functional gene groups associated with the respective phenotype. We hypothesized that functional gene groups between phenotypes are mainly independent from each other. This study will provide additional evidence opposing models that assume 100% pleiotropy (the same ontogenetic factors determine both handedness and language lateralization), but instead is in line with a model of partial pleiotropy (shared and individual ontogenetic factors determine handedness and language lateralization) as suggested by Ocklenburg et al. (2014).

MATERIALS AND METHODS

Identification of Relevant Genes

In order to identify genes associated with handedness or language lateralization, we performed literature search using the database PubMed[1]. Molecular genetic studies were included if performed on human subjects.

We included individual genes previously identified in candidate gene studies on handedness or language lateralization into analysis (Medland et al., 2005; Francks et al., 2007; Bloss et al., 2010; Ocklenburg et al., 2011, 2013a,b; Hampson and Sankar, 2012; Pinel et al., 2012; Arning et al., 2013, 2015;

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[1] https://www.ncbi.nlm.nih.gov/pubmed

Robinson et al., 2016). Furthermore, we included all genes reaching $p < 10^{-5}$ in a GWAS by Scerri et al. (2011) and a GWAS meta-analysis by Brandler et al. (2013). We further included differentially expressed genes from gene expression studies ($p < 0.01$; Sun et al., 2005; Karlebach and Francks, 2015) and top hits identified by family-based genetic association analysis (Savitz et al., 2007) and manual segregation analysis (van Agtmael et al., 2002). Lastly, we included all genes with LOD > 1.5 from a linkage analysis published by Somers et al. (2015). **Table 1** shows the list of 63 genes previously associated with handedness ontogenesis. The list of 45 genes previously associated with the formation of language lateralization is listed in **Table 2**. Importantly, most of these genes do not reach conventional levels of significance or do not replicate. However, it is still likely that GO analysis reveals certain clusters of genes contributing to each of the phenotypes.

Gene Ontology Analysis

We used WebGestalt (WEB-based GEne SeT AnaLysis Toolkit) (Zhang et al., 2005; Wang et al., 2013) to identify shared functional groups of all genes associated with handedness (see **Table 1**). The list containing 63 genes was inserted to WebGestalt to identify GO sets associated with handedness. A GO set is a pre-defined list of genes that share either molecular functions (biochemical activity of a gene product), cellular components (place in the cell where a gene product is active), or biological processes (biological objective of a gene or gene product). For example, the GO set 'determination of left/right symmetry' contains 82 genes and gene products whose biological objective is involved in body formation in a symmetric or asymmetric pattern (Ashburner et al., 2000).

For each GO set, WebGestalt calculated a ratio of enrichment (RE) by comparing the observed number of genes in the inserted gene list and also in the GO set (O) to the expected number of genes in the inserted gene list and also in the GO set (E). This expected value (E) was based on the number of genes in the inserted gene list (L) multiplied with the number of genes in the GO set (GO) and divided by the number of genes in the reference gene set (RG). If the observed value (O) exceeded the expected value (E), the GO set was enriched with a ratio of enrichment $RE = O/E$ (Wang et al., 2013). WebGestalt then used the hypergeometric test to evaluate the significance of enrichment for GO sets in the list of genes. The significance level was set to 0.05 after Benjamini–Hochberg correction for multiple comparisons (Benjamini and Hochberg, 1995). WebGestalt only reported GO sets with corrected p-values smaller than 0.05.

In addition to statistical results, WebGestalt's output included a visualization of relationships between GO sets. This hierarchical structure of GO sets included high level GO sets representing broad molecular functions/cellular components/biological processes, e.g., 'signal transduction (GO:0007165).' These broader GO sets were subdivided into more specific lower level GO sets, e.g., 'regulation of postsynaptic neurotransmitter receptor activity (GO:0098962)' (Ashburner et al., 2000). In order to improve the results' transparency, significant lower level GO sets were clustered in superordinate groups of high level GO sets by visual inspection of this hierarchical structure.

The same procedure was applied on the gene list containing 45 genes associated with ontogenesis of language lateralization (see **Table 2**).

KEGG Pathway Analysis

Using WebGestalt, we performed KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analyses (Kanehisa et al., 2008) to identify biological pathways including genes associated with the gene list of either handedness or language lateralization. Each list of genes (see **Tables 1**, **2**) was entered to WebGestalt separately. KEGG pathways are pre-defined lists of genes that are involved in biological pathways. A RE was calculated for each KEGG pathway analogous to GO analysis. The significance of enrichment for each KEGG pathway was calculated with the hypergeometric test. The significance level was set to 0.05 after Benjamini–Hochberg correction for multiple comparisons (Benjamini and Hochberg, 1995).

Disease Association Analysis

In order to identify diseases associated with gene sets involved in either handedness or language lateralization, we conducted disease association analyses using WebGestalt (Wang et al., 2013). Gene-disease associations were inferred using GLAD4U (Gene List Automatically Derived For You) (Jourquin et al., 2012). Both gene lists (see **Tables 1**, **2**) were entered to WebGestalt separately. A RE was calculated for each disease. The significance of enrichment was calculated using hypergeometric test with a significance level of 0.05 after Benjamini–Hochberg correction (Benjamini and Hochberg, 1995). Using ICD-10 (World Health Organization, 1992), we identified diseases categorized under "V: Mental and behavioral disorders" or "VI: Diseases of the nervous system" as disorders related to the central nervous system (CNS).

RESULTS

Lower Level GO Sets Involved in Handedness and Language Lateralization

After correction for multiple comparisons, GO analysis revealed 64 significant lower level GO sets for the 63 genes associated with handedness, among them 40 biological processes (see **Table 3**), 20 molecular functions, and 4 cellular components (see **Supplementary Figure S1** for full hierarchical GO set overview). Top hits were 'epithelial tube morphogenesis (GO:0060562)' ($p < 0.001$), 'tube development (GO:0035295)' ($p < 0.001$), 'tube morphogenesis (GO: 0035239)' ($p < 0.001$) as well as 'determination of left/right symmetry (GO:0007368)'/'determination of bilateral symmetry (GO:0009855)'/'specification of symmetry (GO:0009799)' (all $p < 0.001$). GO sets with the most genes involved were 'protein binding (GO:0005515)' ($p < 0.05$) with 20 handedness genes involved and 'anatomical structure development (GO:0048856)' ($p < 0.01$) and 'multicellular organismal development (GO:0007275)' ($p < 0.01$) with 18 handedness genes involved.

TABLE 1 | Identified genes involved in handedness ontogenesis.

Gene	Type of association	Reference
Activin receptor type-2B (ACVR2B)	Genome-wide study meta-analysis	Brandler et al., 2013
ADAMTS like 1 (ADAMTSL1)	Genome-wide study meta-analysis	Brandler et al., 2013
Androgen receptor gene (AR)	Candidate gene study	Arning et al., 2015
	Candidate gene study	Hampson and Sankar, 2012
	Candidate gene study	Medland et al., 2005
Androglobin (ADGB)	Genome-wide study meta-analysis	Brandler et al., 2013
Apolipoprotein E (APOE)	Candidate gene study	Bloss et al., 2010
ATP/GTP binding protein like 1 (AGBL1)	Genome-wide association study	Scerri et al., 2011
Breast carcinoma amplified sequence 1 (BCAS1)	Genome-wide association study	Scerri et al., 2011
Calcium voltage-gated channel auxiliary subunit alpha2delta 1 (CACNA2D1)	Genome-wide study meta-analysis	Brandler et al., 2013
Catechol-O-methyltransferase (COMT)	Family-based genetic association analysis	Savitz et al., 2007
Centromere protein C (CENPC1)	Genome-wide study meta-analysis	Brandler et al., 2013
Ceramide kinase (CERK)	Genome-wide study meta-analysis	Brandler et al., 2013
Chromosome 3 open reading frame 20 (C3orf20)	Genome-wide association study	Scerri et al., 2011
Coiled-coil domain containing 102B (CCDC102B)	Genome-wide association study	Scerri et al., 2011
C-type lectin domain family 3 member B (CLEC3B)	Genome-wide association study	Scerri et al., 2011
Dynein, axonemal, heavy chain 13 (DNAHC13)	Manual allele sharing analysis	van Agtmael et al., 2002
E2F transcription factor 8 (E2F8)	Genome-wide study meta-analysis	Brandler et al., 2013
Exosome component 7 (EXOSC7)	Genome-wide association study	Scerri et al., 2011
Feline leukemia virus subgroup C cellular receptor 1 (FLVCR1)	Genome-wide association study	Scerri et al., 2011
Frizzled class receptor 1 (FZD1)	Genome-wide study meta-analysis	Brandler et al., 2013
Fructose-bisphosphatase 2 (FBP2)	Genome-wide association study	Scerri et al., 2011
G protein-coupled receptor kinase 5 (GRK5)	Genome-wide study meta-analysis	Brandler et al., 2013
Gap junction protein alpha 1 (GJA1)	Genome-wide study meta-analysis	Brandler et al., 2013
GLI family zinc finger 3 (GLI3)	Genome-wide study meta-analysis	Brandler et al., 2013
Glypican 3 (GPC3)	Genome-wide study meta-analysis	Brandler et al., 2013
GTP binding protein 10 (GTPBP10)	Genome-wide study meta-analysis	Brandler et al., 2013
Integrin subunit beta 8 (ITGB8)	Genome-wide association study	Scerri et al., 2011
Laminin subunit alpha 5 (LAMA5)	Genome-wide study meta-analysis	Brandler et al., 2013
Latent transforming growth factor beta binding protein 1 (LTBP1)	Genome-wide study meta-analysis	Brandler et al., 2013
Leucine rich repeat transmembrane neuronal 1 (LRRTM1)	Candidate gene study	Francks et al., 2007
LIM domain only 4 (LMO4)	Gene expression study (fetal cortex)	Sun et al., 2005
LOC100132083	Genome-wide association study	Scerri et al., 2011
LOC441204	Genome-wide study meta-analysis	Brandler et al., 2013
Mahogunin ring finger 1 (MGRN1)	Genome-wide study meta-analysis	Brandler et al., 2013
Meiosis specific nuclear structural 1 (MNS1)	Genome-wide study meta-analysis	Brandler et al., 2013
Membrane associated guanylate kinase, WW and PDZ domain containing 1 (MAGI1)	Genome-wide study meta-analysis	Brandler et al., 2013
Microtubule associated scaffold protein 1 (MTUS1)	Genome-wide association study	Scerri et al., 2011
Neogenin 1 (NEO1)	Genome-wide association study	Scerri et al., 2011
Neuromedin B receptor (NMBR)	Genome-wide association study	Scerri et al., 2011
Nodal growth differentiation factor (NODAL)	Manual allele sharing analysis	van Agtmael et al., 2002
Pleiotrophin (PTN)	Genome-wide association study	Scerri et al., 2011
Polycystic kidney disease 2 (PKD2)	Genome-wide study meta-analysis	Brandler et al., 2013
Potassium channel tetramerization domain containing 18 (KCTD18)	Genome-wide association study	Scerri et al., 2011
Potassium sodium-activated channel subfamily T member 2 (KCNT2)	Genome-wide study meta-analysis	Brandler et al., 2013
Prolyl endopeptidase (PREP)	Genome-wide study meta-analysis	Brandler et al., 2013
Proprotein convertase subtilisin/kexin type 6 (PCSK6)	Candidate gene study	Arning et al., 2013
	Genome-wide study meta-analysis	Brandler et al., 2013
	Candidate gene study	Robinson et al., 2016
	Genome-wide association study	Scerri et al., 2011
RAB11 family interacting protein 4 (RAB11FIP4)	Genome-wide study meta-analysis	Brandler et al., 2013
Ras responsive element binding protein 1 (RREB1/HNT)	Genome-wide association study	Scerri et al., 2011

(Continued)

TABLE 1 | Continued

Gene	Type of association	Reference
Regulatory factor X3 (RFX3)	Genome-wide study meta-analysis	Brandler et al., 2013
Replication protein A1 (RPA1)	Genome-wide study meta-analysis	Brandler et al., 2013
Retinoic acid receptor alpha (RARA)	Genome-wide study meta-analysis	Brandler et al., 2013
Ribosomal RNA processing 15 homolog (RRP15)	Genome-wide association study	Scerri et al., 2011
SET domain bifurcated 2 (SETDB2)	Candidate gene study	Ocklenburg et al., 2015a
Signal transducing adaptor family member 1 (STAP1)	Genome-wide study meta-analysis	Brandler et al., 2013
Tachykinin receptor 1 (TACR1)	Genome-wide study meta-analysis	Brandler et al., 2013
Teneurin transmembrane protein 3 (TENM1/ODZ3)	Genome-wide association study	Scerri et al., 2011
Thrombospondin type 1 domain containing 4 (THSD4)	Genome-wide study meta-analysis	Brandler et al., 2013
Transketolase (TKT)	Genome-wide study meta-analysis	Brandler et al., 2013
Transmembrane protein 87B (TMEM87B)	Genome-wide study meta-analysis	Brandler et al., 2013
Tryptophan hydroxylase 2 (TPH2)	Genome-wide association study	Scerri et al., 2011
Tumor protein p63 (TP63)	Genome-wide study meta-analysis	Brandler et al., 2013
UDP glucuronosyltransferase family 2 member B4 (UGT2B4)	Genome-wide study meta-analysis	Brandler et al., 2013
Vesicle trafficking 1 (VTA1)	Genome-wide association study	Scerri et al., 2011
Zinc finger protein 385D (ZNF385D)	Genome-wide study meta-analysis	Brandler et al., 2013

For the 45 genes associated with language lateralization, GO analysis revealed 97 significant lower level GO sets. Among these GO sets were 40 biological processes (see **Table 4**), 29 molecular functions, and 28 cellular components (see **Supplementary Figure S2** for full hierarchical GO set overview). Top hits of GO sets were 'negative regulation of synaptic transmission, glutamatergic (GO:0051967)' ($p < 0.001$), 'feeding behavior (GO:0007631)' ($p < 0.001$), and 'signal release (GO:0023061)' ($p < 0.01$). Most genes were involved in the cellular components 'plasma membrane (GO:0005886)' ($p < 0.05$), 'cell periphery (GO:0071944)' ($p < 0.05$) with 17 genes each and in the biological process 'nervous system development (GO:0007399)' ($p < 0.01$) with 13 genes involved.

Two lower level GO sets concerning cellular components overlap between the gene lists for handedness and language lateralization: 'cell projection (GO:0042995)' ($p < 0.05$) and 'neuron projection (GO:0043005)' ($p < 0.05$). There was no overlap in biological processes.

The distribution of raw *p*-values for all significantly enriched GO sets for handedness and language lateralization is displayed in **Supplementary Figure S3**.

High Level GO Sets Involved in Handedness and Language Lateralization

Visual inspection of the hierarchical relationship between GO sets involved in handedness revealed that significant lower level GO sets regarding biological processes are clustered into three high level GO sets. First, 25 enriched lower level GO sets are involved in anatomical structure development. 'Epithelial tube morphogenesis (GO:0060562)' was the most significantly enriched GO set overall. Lower level GO sets contain not only 'neural tube development (GO:0021915),' but also 'cardiovascular system development (GO:0072358),' 'artery development (GO:0060840),' and 'ureteric bud development (GO:0001657).' Moreover, 6 lower level GO sets involve pattern specification, for example in terms of 'specification of symmetry (GO:0009799),' 'determination of left/right symmetry (GO:0007368),' and 'determination of bilateral symmetry (GO:0009855).' Lastly, 9 lower level GO sets involve biological regulation. These GO sets include 'regulation of developmental process (GO:0050793)' and 'regulation of cell differentiation (GO:0045595).' High level GO sets for genes associated with handedness are visualized in **Supplementary Figure S4**.

In contrast, significant lower level GO sets regarding biological processes in language lateralization are clustered into five high level GO sets. First, 10 enriched lower level GO sets can be described by the high level GO set 'response to stimuli.' These GO sets range from 'feeding behavior (GO:0007631)' to external stimuli like 'behavioral defense response (GO:0002209)' or 'learning (GO:0007612)' and organic substances like 'response to cocaine (GO:0042220).' Second, 3 lower level GO sets are involved in the high level GO set 'nervous system development (GO:0007399),' more specifically 'forebrain development (GO:0030900),' 'telencephalon development (GO:0021537),' and 'nervous system development (GO:0007399).' The third high level GO set with 8 lower level GO sets describes different forms of transport like 'dopamine secretion (GO:0014046),' 'insulin secretion (GO:0030073)' or 'regulation of amine transport (GO:0051952).' The fourth high level GO set includes 10 lower level GO sets involved in signaling, for example 'regulation of transmission of nerve impulse (GO:0051969)' or 'synaptic transmission, glutamatergic (GO:0035249).' Lastly, 9 lower level GO sets describe biological regulation, for example 'regulation of long-term neuronal synaptic plasticity (GO:0048169)' and 'regulation of neurological system process (GO:0031644).' High level GO sets for genes involved in language lateralization are visualized in **Supplementary Figure S4**.

Among the high level GO sets, biological regulation is involved in both handedness and language lateralization (see **Supplementary Figure S4**).

TABLE 2 | Identified genes involved in the ontogenesis of language lateralization.

Gene	Type of association	Reference
5-hydroxytryptamine receptor 1B (HTR1B)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
ADAM metallopeptidase with thrombospondin type 1 motif 4 (ADAMTS4)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
BMP/retinoic acid inducible neural specific 1 (BRINP1)	Linkage analysis	Somers et al., 2015
Cancer susceptibility candidate 15 (CASC15)	Linkage analysis	Somers et al., 2015
Carboxypeptidase A2 (CPA2)	Linkage analysis	Somers et al., 2015
CCR4-NOT transcription complex subunit 4 (CNOT4)	Linkage analysis	Somers et al., 2015
Chloride voltage-gated channel 1 (CLCN1)	Linkage analysis	Somers et al., 2015
Cholecystokinin A receptor (CCKAR)	Candidate gene study	Ocklenburg et al., 2013a
Chromosome 1 open reading frame 95 (C1orf95)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Chromosome 14 open reading frame 132 (C14orf132)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Chromosome 6 open reading frame 142 (C6orf142)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Cytochrome P450 family 27 subfamily A member 1 (CYP27A1)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Deleted in esophageal cancer 1 (DEC1)	Linkage analysis	Somers et al., 2015
Diaphanous related formin 2 (DIAPH2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Dopamine receptor D2 (DRD2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
EPH receptor A6 (EPHA6)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Family with sequence similarity 65, member B (FAM65B)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Forkhead box P2 (FOXP2)	Candidate gene study	Ocklenburg et al., 2013b
	Candidate gene study	Pinel et al., 2012
Galanin and GMAP prepropeptide (GAL)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Glutamate ionotropic receptor kainate type subunit 2 (GRIK2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B)	Candidate gene study	Ocklenburg et al., 2011
Glycine receptor alpha 2 (GLRA2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Glypican 4 (GPC4)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Hippocalcin (HPCA)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Hyaluronan and proteoglycan link protein 4 (HAPLN4)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
KIAA0319	Candidate gene study	Pinel et al., 2012
Long intergenic non-protein coding RNA, p53 induced transcript (LINC-PRINT)	Linkage analysis	Somers et al., 2015
Neurofilament heavy (NEFH)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Neuronal differentiation 1 (NEUROD1)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Nuclear receptor subfamily 2 group F member 2 (NR2F2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Parvalbumin (PVALB)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Plexin C1 (PLXNC1)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Potassium channel tetramerization domain containing 4 (KCTD4)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Protein tyrosine phosphatase, non-receptor type 3 (PTPN3)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Protein tyrosine phosphatase, receptor type R (PTPRR)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Regulator of G-protein signaling 8 (RGS8)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
RNA binding motif protein 33 (RBM33)	Linkage analysis	Somers et al., 2015
SGK2, serine/threonine kinase 2 (SGK2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Sodium voltage-gated channel alpha subunit 3 (SCN3A)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Solute carrier family 6 member 9 (SLC6A9)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Synaptotagmin 2 (SYT2)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
THEM2	Candidate gene study	Pinel et al., 2012
TTRAP	Candidate gene study	Pinel et al., 2012
Yippee like 1 (YPEL1)	Gene expression study (adult cortex)	Karlebach and Francks, 2015
Zinc finger CCHC-type containing 12 (ZCCHC12)	Gene expression study (adult cortex)	Karlebach and Francks, 2015

KEGG Pathway Analysis

For genes involved in handedness, KEGG analysis yielded six KEGG pathways significantly enriched after correction for multiple comparisons: 'Pathways in cancer' ($p < 0.001$), 'Basal cell carcinoma' ($p < 0.01$), 'ECM-receptor interaction' ($p < 0.01$), 'TGF-beta signaling pathway' ($p < 0.01$), 'Cell adhesion molecules (CAMs)' ($p < 0.01$), and 'Focal adhesion' ($p < 0.05$).

For genes involved in language lateralization, KEGG analysis yielded four KEGG pathways significantly enriched after correction for multiple comparisons: 'Neuroactive ligand-receptor interaction' ($p < 0.001$), 'Amyotrophic lateral sclerosis (ALS)' ($p < 0.01$), 'Pancreatic secretion' ($p < 0.001$), and 'Axon guidance' ($p < 0.01$). The distribution of corresponding raw *p*-values is displayed in **Supplementary Figure S3**.

TABLE 3 | Lower level and high level gene ontology (GO) sets enriched in genes associated with handedness ontogenesis.

Lower level GO set	GO ID	Number of genes involved	*P*-value	High level GO set
Epithelial tube morphogenesis	GO:0060562	8	9.6×10^{-6}	Anatomical structure development
Tube development	GO:0035295	9	2.2×10^{-5}	
Tube morphogenesis	GO:0035239	8	2.2×10^{-5}	
Morphogenesis of an epithelium	GO:0002009	8	6.7×10^{-5}	
Circulatory system development	GO:0072359	10	7.3×10^{-5}	
Cardiovascular system development	GO:0072358	10	7.3×10^{-5}	
Embryonic morphogenesis	GO:0048598	8	0.0002	
Anatomical structure formation involved in morphogenesis	GO:0048646	13	0.0002	
Tissue morphogenesis	GO:0048729	8	0.0002	
Neural tube development	GO:0021915	5	0.0003	
Tissue development	GO:0009888	12	0.0003	
Heart development	GO:0007507	7	0.0003	
Embryo development	GO:0009790	10	0.0003	
Morphogenesis of embryonic epithelium	GO:0016331	5	0.0003	
Epithelium development	GO:0060429	8	0.0005	
Organ development	GO:0048513	15	0.0007	
Chordate embryonic development	GO:0043009	7	0.0012	
Ureteric bud development	GO:0001657	4	0.0012	
Vasculature development	GO:0001944	7	0.0012	
Anatomical structure morphogenesis	GO:0009653	13	0.0013	
Embryo development ending in birth or egg hatching	GO:0009792	7	0.0013	
System development	GO:0048731	17	0.0014	
Anatomical structure development	GO:0048856	18	0.0017	
Organ morphogenesis	GO:0009887	8	0.0017	
Artery development	GO:0060840	3	0.0017	
Determination of left/right symmetry	GO:0007368	5	6.7×10^{-5}	Pattern specification
Determination of bilateral symmetry	GO:0009855	5	7.3×10^{-5}	
Specification of symmetry	GO:0009799	5	7.3×10^{-5}	
Pattern specification process	GO:0007389	7	0.0005	
Cell fate commitment	GO:0045165	5	0.0014	
Multicellular organismal development	GO:0007275	18	0.0017	
Determination of heart left/right asymmetry	GO:0061371	3	0.0017	
Regulation of cell differentiation	GO:0045595	10	0.0005	Biological regulation
Cell fate specification	GO:0001708	4	0.0005	
Regulation of embryonic development	GO:0045995	4	0.0006	
Regulation of developmental process	GO:0050793	11	0.0012	
Positive regulation of nitrogen compound metabolic process	GO:0051173	10	0.0013	
Regulation of protein import into nucleus	GO:0042306	4	0.0017	
Regulation of protein localization to nucleus	GO:1900180	4	0.0017	
Regulation of intracellular protein transport	GO:0033157	4	0.0029	

P-values are corrected for multiple comparisons using Benjamini–Hochberg correction.

Disease Association Analysis

Genes associated to handedness ontogenesis were involved in 156 diseases, among them 61 CNS-related diseases (39.10%). The most significantly enriched diseases were 'Craniofacial Abnormalities' ($p < 0.001$), 'Amnesia' ($p < 0.001$), and 'Bone Diseases, Developmental' ($p < 0.01$). Most genes were involved in 'Craniofacial Abnormalities' ($p < 0.001$) and 'Congenital Abnormalities' ($p < 0.01$) (six genes involved) and 'Gilbert Disease' ($p < 0.01$), 'Epithelial cancers' ($p < 0.01$), 'Musculoskeletal Abnormalities' ($p < 0.01$), and 'Cancer or viral infections' ($p < 0.05$) with five genes involved.

Genes involved in language lateralization were mostly associated to CNS-related diseases. 81 of 94 (86.17%) significantly enriched diseases were involved in mental or psychiatric states. The disease categories 'Mental Disorders' ($p < 0.001$), 'Substance-Related Disorders' ($p < 0.001$), and 'Alcoholism' ($p < 0.001$) were most significantly enriched. 'Mental Disorders' ($p < 0.001$) was enriched with 10 genes involved in language lateralization, followed by 'Substance-Related Disorders' ($p < 0.001$) and 'Nervous System Diseases' ($p < 0.001$) with seven genes involved. Associations between diseases and gene lists were much stronger in terms of *p*-values for genes involved in language lateralization

TABLE 4 | Lower level and high level GO sets enriched in genes associated with the ontogenesis of language lateralization.

Lower level GO set	GO ID	Number of genes involved	*P*-value	High level GO set
Feeding behavior	GO:0007631	5	0.0005	Response to stimulus
Response to cocaine	GO:0042220	3	0.0024	
Response to tropane	GO:0014073	3	0.0024	
Auditory behavior	GO:0031223	2	0.0030	
Behavior	GO:0007610	7	0.0052	
Mechanosensory behavior	GO:0007638	2	0.0052	
Response to ammonium ion	GO:0060359	3	0.0052	
Startle response	GO:0001964	2	0.0127	
Behavioral defense response	GO:0002209	2	0.0132	
Learning	GO:0007612	3	0.0132	
Forebrain development	GO:0030900	6	0.0030	Nervous system development
Nervous system development	GO:0007399	13	0.0039	
Telencephalon development	GO:0021537	4	0.012	
G-protein coupled receptor internalization	GO:0002031	2	0.0074	Transport
Regulation of amine transport	GO:0051952	3	0.0094	
Regulation of dopamine secretion	GO:0014059	2	0.012	
Dopamine secretion	GO:0014046	2	0.012	
Growth hormone secretion	GO:0030252	2	0.012	
Insulin secretion	GO:0030073	4	0.012	
Peptide hormone secretion	GO:0030072	4	0.013	
Peptide secretion	GO:0002790	4	0.013	
Negative regulation of synaptic transmission, glutamatergic	GO:0051967	3	0.0004	Signaling
Signal release	GO:0023061	7	0.0019	
Generation of a signal involved in cell-cell signaling	GO:0003001	7	0.0019	
Regulation of transmission of nerve impulse	GO:0051969	5	0.0039	
Synaptic transmission, glutamatergic	GO:0035249	3	0.0052	
Negative regulation of G-protein coupled receptor protein signaling pathway	GO:0045744	3	0.011	
Negative adaptation of signaling pathway	GO:0022401	2	0.012	
Desensitization of G-protein coupled receptor protein signaling pathway	GO:0002029	2	0.01	
Adaptation of signaling pathway	GO:0023058	2	0.013	
Negative regulation of protein kinase B signaling cascade	GO:0051898	2	0.013	
Regulation of long-term neuronal synaptic plasticity	GO:0048169	3	0.0020	Biological regulation
Regulation of synaptic transmission, glutamatergic	GO:0051966	3	0.0030	
Negative regulation of synaptic transmission	GO:0050805	3	0.0039	
Negative regulation of transmission of nerve impulse	GO:0051970	3	0.0039	
Negative regulation of neurological system process	GO:0031645	3	0.0052	
Regulation of neuronal synaptic plasticity	GO:0048168	3	0.0052	
Regulation of neurological system process	GO:0031644	5	0.0052	
Regulation of system process	GO:0044057	6	0.012	
Regulation of synaptic transmission	GO:0050804	4	0.013	

P-values are corrected for multiple comparisons using Benjamini–Hochberg correction.

than for genes involved in handedness (see **Supplementary Figure S3**).

There was considerable overlap in the enriched diseases for genes involved in handedness and language lateralization. Forty-two diseases were involved in both phenotypes, among them 39 (92.86%) CNS-related diseases.

DISCUSSION

Handedness and language lateralization have been proposed to share a common ontogenetic basis (Annett, 1975), but single genes involved in the formation of both phenotypes have not been identified (Ocklenburg et al., 2014). Here we show that the GO sets enriched in language lateralization barely overlap with those found for handedness. Thus, in addition to the fact that individual genes involved in handedness and language lateralization development are independent from each other, functional gene products also differ fundamentally with no shared biological processes. This indicates different functional cascades underlying handedness and language lateralization.

For genes involved in ontogenesis of handedness, significant lower level GO sets of biological processes are clustered into three high level GO sets (see **Supplementary Figure S4**). First, most lower level GO sets describe anatomical structure development in different body parts. This implies that genes involved in handedness development exert their effect at an early embryonic stage and their functional gene products do not only contribute to the CNS, but also to the whole body. This is in line with the suggestion by Brandler et al. (2013), who claim that handedness is partially controlled by the molecular mechanisms that establish body asymmetry during early development. This finding has been supported by neuroimaging studies of patients with situs inversus, who displayed atypical patterns of frontal and occipital cerebral asymmetries (Kennedy et al., 1999; Ihara et al., 2010). However, situs inversus patients display the standard pattern of handedness, which rather supports a dissociation between visceral and brain asymmetries (Matsumoto et al., 1997; McManus et al., 2004; Afzelius and Stenram, 2006). It might be that genes associated with handedness are not necessarily involved in body asymmetry formation, but rather in anatomical structure development *per se*. Interestingly, most of the significant lower level GO sets involved in anatomical structure development include the *androgen receptor (AR)* gene. Prenatal testosterone has been shown to affect handedness and language lateralization in opposite directions (Lust et al., 2011). Our findings suggest that the capacity of binding testosterone in the developing fetal brain might induce differences in anatomical structure development that affect handedness, but not language lateralization. This finding is highly interesting in the context of sex differences in hemispheric asymmetries. While it is more or less undisputed that there is a 1.23 higher rate of male compared to female left-handers (Papadatou-Pastou et al., 2008), there are not necessarily sex differences in language lateralization (McManus, 2010). If that is the case, the findings from GO analysis may contribute to the explanation of this effect. Another high level GO set involved in handedness development is ‘pattern specification process (GO:0007389).’ As expected, the significant GO sets indicate the involvement of handedness genes on symmetry and asymmetry development. This result comes to no surprise, as there may likely be an ascertainment bias, since several of the original studies were candidate gene studies. Interestingly, KEGG pathway analysis revealed that genes involved in handedness ontogenesis are associated to the TGF-beta signaling pathway involved in bodily left-right asymmetry (Mittwoch, 2008; Shiratori and Hamada, 2014). While *ACVR2B* is involved in gonadal growth, embryo differentiation, and placenta formation, *NODAL* is involved in left-right axis determination and mesoderm and endoderm induction (see **Supplementary Figure S5**). This finding indicates an involvement of the TGF-beta signaling pathway on handedness ontogenesis at an early stage of development. In a recent study, asymmetrical gene expression was found between left and right human spinal cord at 8 weeks post conception. Besides DNA methylation patterns, gene expression asymmetries were epigenetically regulated by miRNAs involved in the TGF-beta signaling pathway. Since preliminary forms of handedness are already visible at this time point before the spinal cord and the motor cortex are functionally connected, the TGF-beta signaling pathway might have an impact on early behavioral asymmetries in arm movements (Ocklenburg et al., 2017). This in line with our finding that the TGF-beta signaling pathway is involved in handedness, but not in language lateralization. The last high level GO set of biological processes enriched in handedness genes is comprised of biological regulation, for example on developmental processes as well as cell differentiation. This indicates a regulatory function of genes associated with handedness on all levels of developmental control and cell fate determination.

For genes involved in ontogenesis of language lateralization, four high level GO sets were identified. Many lower level GO sets describe responses to different stimuli. Especially the role of the GO sets ‘startle response (GO:0001964)’ and ‘behavioral defense response (GO:0002209)’ are in line with a relation between stress and the ontogenesis of hemispheric asymmetries that has been reported in many vertebrate species (see Ocklenburg et al., 2016). It has been shown that both acute and chronic stress can affect different forms of lateralization in the human brain. Our findings here suggest that genetic predispositions for certain response patterns may also play a role in the ontogenesis of language lateralization, implying a role for gene-environment interactions during asymmetry development. Another highly interesting GO set involved in the formation of language lateralization is ‘learning (GO:0007612).’ Compared to handedness, language is more closely related to cognition, which is in line with the role of genes associated with language lateralization on neuronal signaling, e.g., neurotransmitters like glutamate and dopamine (Ocklenburg et al., 2011, 2013a). Also, the involvement of learning processes in the ontogenesis of language lateralization (Thomas et al., 1997) indicates a greater role of neuronal plasticity processes for this phenotype than for handedness. Secondly, lower level GO sets are involved in nervous system development. Compared to GO sets enriched in genes involved in handedness, which comprise cerebral, but also body development, this result suggests that genes involved in language lateralization are specifically engaged within the CNS. This is also supported by our finding that genes involved in language lateralization are significantly enriched in the axon guidance pathway including *EPHA6* and *PLXNC1*, two receptors involved in axonal outgrowth, repulsion and attraction (see **Supplementary Figure S6**). In addition to their effect on basic cell metabolic processes, genes associated with language lateralization seem to be involved in neuronal signaling. ‘Negative regulation of G-protein coupled receptor protein signaling pathway (GO:0045744)’ or ‘desensitization of G-protein coupled receptor protein signaling pathway (GO:0002029)’ are important lower level GO sets within this category. The G-protein coupled receptor protein signaling pathway has been identified as asymmetrically expressed in adult human language related areas: Superior Temporal Gyrus (STS) and Heschl’s Gyrus (HG). Moreover, in our study many GO sets are involved in transmission of nerve impulse, a GO set asymmetrically expressed in STS, but not in HG (Karlebach and Francks, 2015). Lastly, lower level GO sets significantly enriched in genes associated with language lateralization are involved in the high level GO set of biological regulation. Although individual GO sets of language lateralization and handedness do not overlap in terms of biological processes, biological regulation represents a high level GO set within genes involved in both phenotypes. This can be considered as a minimal overlap between biological processes of gene products involved in handedness and those involved in language lateralization.

Overall, gene lists for handedness and language lateralization resulted in similar numbers of enriched GO sets. However, the distribution of genes differed between phenotypes. For genes associated with handedness, there were many GO sets with 10 or more genes enriched in. Thus, products of genes involved in handedness formation seems to be less complex compared to products of genes involved in language lateralization. The latter are more heterogenous with maximally seven genes enriched in the same GO set (with the exception of 'nervous system development (GO:0007399)' with 13 genes enriched) and less strong associations in terms of *p*-values.

In contrast, associations between diseases and gene lists were much stronger for genes involved in language lateralization than for genes involved in handedness. For language lateralization, many disease categories were enriched with high numbers of genes involved, mostly categorized in mental and neurological diseases. Among the diseases significantly associated with genes involved in language lateralization are schizophrenia (Ocklenburg et al., 2013e, 2015b) and autism spectrum disorders (Knaus et al., 2010; Tager-Flusberg, 2016). Language lateralization seems more strongly connected to disorders of neurological system development, which is completely in line with our finding that associated genes are enriched in nervous system development rather than anatomical structure development. In contrast, genes associated with handedness ontogenesis are involved in diseases affecting the whole body, which supports our findings from GO analyses and the argumentation pointed out by Brandler et al. (2013). Among the significantly enriched diseases were many that had been associated with handedness before, specifically depression (Denny, 2009), bipolar disorder (Nowakowska et al., 2008), language and learning disorders (Geschwind and Behan, 1982), anxiety disorders (Logue et al., 2015), attention deficit hyperactivity disorder (Brandler and Paracchini, 2014), and schizophrenia (Hirnstein and Hugdahl, 2014).

Our results support the idea of a model of partial pleiotropy for handedness and language lateralization as suggested by Ocklenburg et al. (2014). However, biological and statistical issues remain to be solved: First, two or more lists of genes could result in different GO sets that might still be highly intercorrelated and therefore related to one another. However, this may rather concern low level GO sets. In our data, high level superordinate GO sets between phenotypes are distinct from each other, but this limitation should nonetheless be kept in mind. Second, since most of the included genes of both lists do not reach conventional levels of significance or do not replicate in association studies or GWASs we cannot rule out that statistical noise could have had an impact on the results. Low pleiotropy between genes associated with handedness and language lateralization could therefore partly represent measurement error.

Taken together, our findings further suggest that handedness and language lateralization are ontogenetically independent, complex phenotypes (Ocklenburg et al., 2014). Relative independence of these phenotypes has also recently been concluded in terms of genetic background (Corballis, 2017) as well as in terms of neuroanatomy (Króliczak et al., 2016). Compared to genes involved in handedness ontogenesis, which mostly contribute to structural development, genes involved in language lateralization rather contribute to activity-dependent cognitive processes partly associated to mental and neurological disorders. When searching for overlapping genetic contributions to the ontogenesis of these two traits, our results indicate that particularly genes within the high level GO set of 'biological regulation' may represent promising candidate genes. Revealing further candidate genes for handedness and language lateralization will not only contribute to important insights into the development of hemispheric asymmetries, but also to a better understanding of disorders related to atypical lateralization, e.g., schizophrenia (Levchenko et al., 2014).

AUTHOR CONTRIBUTIONS

JS performed data collection, analyzed data and wrote the manuscript, SL analyzed data, RK analyzed data, OG designed the study, and SO designed the study. All authors discussed the results and edited the manuscript.

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SUPPLEMENTARY MATERIAL

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FIGURE S1 | Full hierarchical GO set overview for genes involved in handedness ontogenesis.

FIGURE S2 | Full hierarchical GO set overview for genes involved in the ontogenesis of language lateralization.

FIGURE S3 | Distribution of raw *p*-values for all significant lower level GO sets involved in handedness and language lateralization.

FIGURE S4 | High level GO sets involved in handedness and language lateralization.

FIGURE S5 | Output of KEGG analysis for the TGF-beta signaling pathway. Genes involved in handedness ontogenesis are highlighted in red.

FIGURE S6 | Output of KEGG analysis for the axon guiding pathway. Genes involved in language lateralization are highlighted in red.

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frontiers in Neuroscience

ORIGINAL RESEARCH
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Effect of Constrained Arm Posture on the Processing of Action Verbs

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Evidence is increasing that brain areas that are responsible for action planning and execution are activated during the information processing of action-related verbs (e.g., *pick* or *kick*). To obtain further evidence, we conducted three experiments to see if constraining arm posture, which could disturb the motor planning and imagery for that arm, would lead to delayed judgment of verbs referring to arm actions. In all experiments, native Japanese speakers judged as quickly as possible whether the presented object and the verb would be compatible (e.g., *ball–throw*) or not (e.g., *ball–pour*). Constrained arm posture was introduced to the task by asking participants to keep both hands behind their back. Two types of verbs were used: manual action verbs (i.e., verbs referring to actions performed on an object by a human hand) and non-manual action verbs. In contrast to our hypothesis that constrained arm posture would affect only the information processing of manual action verbs, the results showed delayed processing of both manual action and non-manual action verbs when the arm posture was constrained. The effect of constrained arm posture was observed even when participants responded with their voice, suggesting that the delayed judgment was not simply due to the difficulty of responding with the hand (i.e., basic motor interference). We discussed why, contrary to our hypothesis, constrained arm posture resulted in delayed CRTs regardless of the "manipulability" as symbolized by the verbs.

Keywords: embodied language, cognition, peripheral bodily state, language, action-related verb

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INTRODUCTION

Several lines of evidence show that brain regions that are involved in motor planning and execution are also involved in the semantic processing of language stimuli (Aziz-Zadeh and Damasio, 2008; Pulvermüller and Fadiga, 2010; Willems and Casasanto, 2011). The first line of evidence comes from brain imaging and neurophysiological studies. Brain areas that are activated while performing finger movements are also activated when individuals passively read words regarding arm actions (Hauk et al., 2004). Premotor areas, which play a role in planning movements and in the sensory guidance of movements, are activated during the semantic processing of action-related words (Hauk et al., 2004; Shtyrov et al., 2004; Pulvermüller et al., 2005; Tettamanti et al., 2005; Aziz-Zadeh et al., 2006; Raposo et al., 2009; Willems et al., 2011; Michael et al., 2014). Buccino et al. (2005) used transcranial magnetic stimulation to assess whether listening to action-related sentences modulates the activity of the primary motor cortex. The results showed that motor activity in the primary motor cortex was elicited soon after the presentation of action-related sentences and that stimulation of that region at early latencies interfered with language task performance. These results hint at the involvement of brain areas responsible for action planning and execution in information processing for action-related words.

Behavioral studies showed evidence along the same lines (Glenberg and Kaschak, 2002; Boulenger et al., 2008, 2009; Dalla Volta et al., 2009; Aravena et al., 2010; Rueschemeyer et al., 2010; Springer and Prinz, 2010; Costantini et al., 2011; Ambrosini et al., 2012; Liepelt et al., 2012; van Dam et al., 2014). For example, in one study (Glenberg and Kaschak, 2002), participants were asked to judge whether a sentence was semantically meaningful. The response involved moving the index finger from the resting position to either a button located away from the trunk or a button located closer to the trunk. The results showed that, when a sentence implied manual action whereby the hand would move away from the trunk (e.g., "Put your finger under the faucet"), participants' responses were delayed when the response involved moving the finger closer to the trunk. The authors reasoned that action-related sentences referring to movement in a particular direction are processed by brain areas that are also responsible for planning and executing that action. As a result, movement execution in the opposite direction was delayed. In another study (Ambrosini et al., 2012), participants were asked to judge as quickly as possible whether a presented object and a verb were compatible, meaning that the action symbolized by the verb could be sensibly carried out on the object. If the object and the verb were judged to be compatible, participants were asked to lift the right index finger from a response button and then mimic a reach-to-grasp movement toward the computer screen. The results showed that judging the compatibility between object and verb was faster when the verb was related to the actual manipulation of that object than when the verb was related to simply observing the object (e.g., *to look*), and when the verb was related to the pointing toward the object (e.g., *to point*). These results suggest that there is likely an overlap between systems involved in information processing of action-related verbs, and perceptual-motor systems that are recruited during performance of that same action.

Neuropsychological studies showed that selective deficits exist in the processing of action-related words following lesions in motor regions of the brain (Bak et al., 2001; Neininger and Pulvermüller, 2003; Mahon and Caramazza, 2005). Neininger and Pulvermüller (2003) demonstrated that patients with lesions in the right frontal lobe (including primary motor and premotor areas) showed severe deficits in processing action verbs. Most patients had left hemiparesis. The experimental task was a lexical decision task in which participants determined as quickly as possible whether a presented letter string was a real word or a meaningless pseudoword. The words presented were either concrete nouns with strong visual associations (e.g., *cat*), concrete nouns with strong visual and motor associations (e.g., *train*), or action verbs that caused strong motor associations (e.g., *write*). The results showed that patients had more errors for action verbs than for other types of words. This suggests that motor dysfunction patients were also impaired in action-verb language processing, even in the absence of specific speech disorders.

The above studies show that neural systems subserving language and neural systems subserving motor control are strongly coupled. There is evidence in the field of mental imagery that when the arm is temporally prevented from moving, this can have a negative effect on the ability to perform various imagery tasks. For example, short-term (24 h) limb immobilization led to reduced performance in mental rotation (Meugnot et al., 2014). In another study, the duration of the motor imagery of hand movement was prolonged during load attachment to the arm (Cerritelli et al., 2000). Following the same logic, we reasoned that restriction of arm movements could lead to delayed processing of verbal material relating to manual activities. To our knowledge, this straightforward behavioral intervention has never been used in the field of language processing and might thus be used as a heuristic to further investigate whether changes in action capabilities have an impact on cognition.

A relevant study showed that patients who had suffered spinal cord inflammation and resultant neurological deficits (peripheral or musculoskeletal system impairment) had preserved information processing abilities regarding action-related words (Cardona et al., 2014). Although these findings seem to be inconsistent with our expectation, the major issue of the patients was not peripheral body status but impairment of the central nervous system Therefore, testing the effect of constraining limbs in individuals with no neurological or peripheral deficits is necessary to directly test this issue. Note that patients with neurological deficits are characterized by prolonged and profound changes in action capabilities, which tend to lead to neural reorganization (either via compensation or restitution). As a result, it can be difficult to disentangle (short-lived) embodiment effects from (longer lasting) neuroplasticity. Therefore, testing the direct effects of changes in the motor periphery (in our case, constraining motor degrees of freedom via the restriction of arm posture) in individuals with no neurological or peripheral deficits is necessary to directly test this issue.

As an aside, it is unclear whether the motor system is causally involved in language (this was dubbed the "necessity question" by van Elk et al., 2010). Authors such as Pulvermüller and colleagues (e.g., Pulvermüller and Fadiga, 2010) have defended the claim that the motor system plays an active role in language comprehension. However, according to others (e.g., Mahon and Caramazza, 2008), observed motor activity (neural or behavioral) might simply be an epiphenomenon, reflecting activation in sensorimotor systems following full-blown language processing. Our aim in this paper is not to provide evidence for or against either perspective. Rather, we aim to utilize a behavioral paradigm that has rarely been used and that might shed light on the question of whether, and to what extent, the state of the motor system influences cognition.

We conducted three experiments. In all experiments, participants judged as quickly and accurately as possible whether a verb and a picture of an object were compatible or incompatible. Since participants had to select one of two responses (depending on judged compatibility) this task constitutes a choice reaction time task (CRT). For the purpose of a more informative description of the task, this task was referred to as a compatibility judgment task. We tested whether constraining arm posture, resulting in a temporary elimination of afforded manual actions, would lead to delayed judgment. To test this hypothesis, two types of verbs were used: manual action (MA) verbs (i.e., verbs referring to actions performed on an object by a human hand) and non-manual action (non-MA) verbs (verbs that do not involve manipulation). We hypothesized that constrained arm posture would affect only the information processing of the MA verbs, relative to the non-MA verbs. The differences between the three experiments involved the response method (finger movements in Experiments 1 and 3 and verbal utterances in Experiment 2) and the order of presenting the object–verb pairs (an object was presented first in Experiments 1 and 2, whereas a verb was presented first in Experiment 3). To confirm that delayed responses would not be caused simply by motor factors of body constraints (e.g., difficulty or discomfort when pushing the button), we also examined the effect of constraining the arm in a task where no stimulus classification had to take place. Participants simply had to push one response button as quickly as possible, in response to the onset of the visual stimulus. Since no stimulus or response selection had to take place, this task constitutes a simple reaction time task (SRT), and in the present paper we refer to it as a word detection task.

GENERAL METHODS

Visual Stimuli

Each trial involved the sequential presentation of a 3D object image and a verb (see **Figure 1**). The 3D object images were created using 3D-modeling software (MAYA, Autodesk, USA). This software allows one to create real-world scaled images. Each image depicted a table with an object placed on top of it. The dimensions and location of each object relative to those of the table were determined as if the object were within the participants' peripersonal space (approximately 30 cm). Ten objects that were manipulable with a single hand were selected (see **Table 1**, left column).

We used 40 unique Japanese verbs, falling into four different categories according to verb type (MA and non-MA) and compatibility (compatible and incompatible, see **Table 1**). MA verbs were all transitive verbs, whereas non-MA verbs were all intransitive verbs. As an example, the stimulus-verb pair of "knife" and "cut" (MA verb) was considered compatible. The compatibility of a verb with each object had been determined on the basis of a preliminary study using a questionnaire. In this preliminary study, we preselected (a) 18 verbs relating to manual action, and are apparently compatible with at least one of the 10 objects and (b) 18 verbs which relates to non-manual action and are apparently compatible with at least one of the 10 objects. For each of 10 objects, 13 Japanese speakers were asked to select all manual action and non-manual action verbs that they considered to be compatible. Based on the results of the preliminary study, verbs that were regarded as compatible with a respective object by all participants (or 12 of 13 participants for the *hammer–fall* combination) were used as compatible verb–object pairs. In contrast, verbs that none of the participants regarded as compatible with a respective object were used as incompatible verb-object pairs.

Notably, some of object–verb pairs were based on the relationship between an instrumental object and the verb which is suitable for expressing the use of the instrumental object. We selected some object–verb pairs based on such relationship because we noticed that it was much easier for participants to judge compatibility.

Task, Apparatus, and Procedure

Two experimental tasks were performed using Presentation 17.1 (Neurobehavioral Systems, Inc., USA). The main experimental task was a compatibility judgment task. Participants sat in front of a computer monitor (512 × 289 mm; FS2333, EIZO, Japan) at a distance of 40 cm from the monitor and gave compatibility judgments (see below). The apparatus for measuring response time differed between experiments. In Experiments 1 and 3, in which a response by the index finger was requested, a response box with four buttons (4 Button Curve Right, Current Designs, Inc., USA) was used. In Experiment 2 in which a vocal response was requested, a voice key (SV-1, Cedrus, USA) was used.

The details of the sequential presentation in each trial are as follows (see **Figure 1**). A cross mark (font size 80) appeared for 1500 ms (used as a fixation point). An image of a 3D object was then presented for 500 ms. As soon as the object image disappeared, a cross mark appeared again for 50–250 ms, followed by the presentation of a verb. The verb disappeared either when participants responded or when the duration of no response exceeded 1500 ms. Participants were asked to judge as quickly as possible whether the combination of object and verb was compatible or incompatible. Participants performed this task under two hand-position conditions: normal and constrained (see **Figure 2**). Under the normal condition, participants put both hands in front of them on a table and operated the response buttons with both index fingers. Under the constrained condition, we asked participants to push buttons that were attached to the back support of a chair. This arrangement thus constrained participant's hand positions and arm postures. Which of the two buttons had to be pushed for a compatible pair was counterbalanced: when participants determined that the object and the verb were compatible, half of the participants were asked to lift the left finger, while the other half were asked to lift the right finger.

The other task was a word detection task. This task was necessary to determine whether the constrained posture *per se* would affect response times (i.e., the response could be delayed due to the motor factor). The same stimuli as in the compatibility judgment task were used. Participants were asked to react as quickly as possible when the verb was presented.

Each of the three experiments consisted of three parts: a preliminary check of the compatibility between the objects and verbs, the compatibility judgment task, and the word detection task. All participants performed these tasks in the same order. The compatibility judgment task was performed before the word detection task to avoid the possibility that exposure to the stimuli in the word detection task could affect response times in the compatibility judgment task. The preliminary check was necessary to confirm that all words selected as compatible were also judged to be compatible by the participants in each

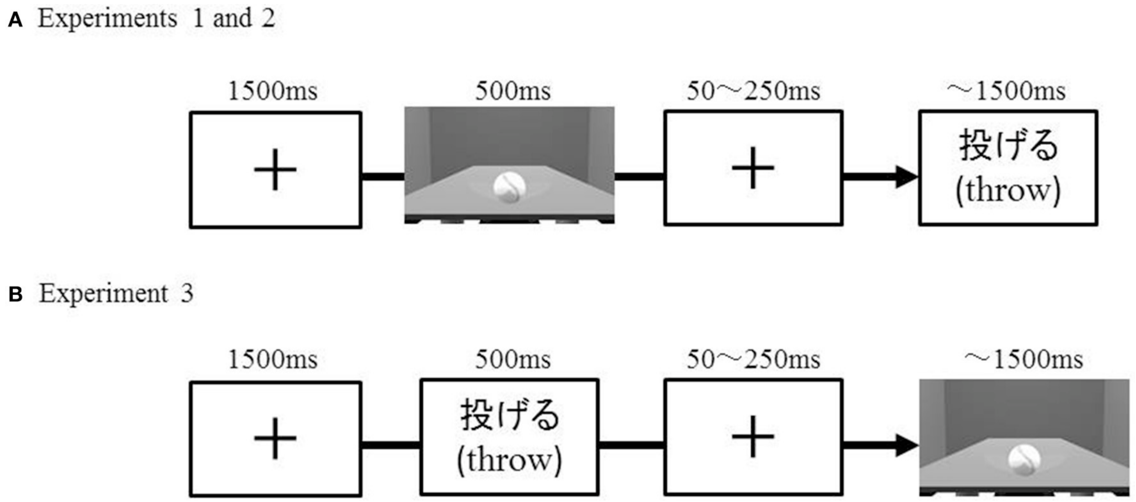

FIGURE 1 | Example of experiment stimuli (this trial represents a compatible combination) presented in Experiments 1 and 2 (A) and Experiment 3 **(B)**.

experiment. The results of this preliminary study showed that one or two words were not classified as compatible by one or two participants (*fall* for *can* and *hammer* in Exp. 1, *fall* for *hammer* in Exp. 2, and *fall* for *hammer* in Exp. 3). In such cases, participants were asked to treat these words as compatible.

The number of trials for the compatibility judgment task was 400: five trials for 10 objects × four verbs × two hand positions. The number of trials for the word detection task was 240: three trials for 10 objects × four verbs × two hand positions. The reason for setting a smaller number of trials for the word detection task was as follows. The word detection task was intended purely to establish a baseline of motor performance, regardless of response selection and regardless of stimulus processing. It served only to highlight the fact that, even with the hands being located behind the back, responses are equally fast. We used a smaller number of trials for the word detection task than for the compatibility judgment task in the expectation of a smaller variability for the word detection task. This was also helpful to reduce the risk that performance of the word detection task was affected by fatigue (the word detection task was always performed after the compatibility judgment task).

For both tasks, the trials were divided into two blocks depending on the hand-position condition. The order in which the hand-position condition was tested was counterbalanced among the participants. A rest period of about 3 min was scheduled within each block.

Data Analysis

The dependent variables for the compatibility judgment task were the mean reaction time and error rate; for the word detection task only the mean reaction time was calculated. We performed a three-way repeated measures analysis of variance (ANOVA) with the following factors: (a) object–verb compatibility (compatible or incompatible), (b) verb type (manual action or non-manual action), and (c) hand position (unconstrained or constrained). In addition, to investigate whether constrained arm posture would affect only the CRT obtained in the compatibility judgment task, we also performed a two-way, task type (compatibility judgment task and word detection task) and hand position (constrained or unconstrained), ANOVA with repeated measures on both factors. Significant main and interaction effects were analyzed further using Bonferroni-corrected pairwise comparisons.

EXPERIMENT 1

We examined whether constrained arm posture would lead to the delayed judgment of verbs referring to arm actions in Experiment 1. Based on previous findings, we predicted that delayed judgment by constrained arm posture would be observed particularly for MA verbs but not for non-MA verbs because only MA verbs are related to manual actions.

Method

Eighteen right-handed, young Japanese individuals participated (nine females and nine males, mean age = 27.5, *SD* = 6.3). Written, informed consent was obtained from each participant prior to the experiment. The protocol was approved by the ethics committee at the Tokyo Metropolitan University in accordance with the Declaration of Helsinki (authorization number H27-15). Responses were made by lifting the left or right index finger. The buttons located at the right and left edges of the response box, which contained four buttons, were used for measuring the response. Each trial began with the participant resting the right and left index finger on the right and left buttons, respectively. The participants determined whether the object and the verb were compatible or incompatible. Half of the participants lifted the right finger when an object–verb pair was compatible, whereas they lifted the left finger when a pair was incompatible. The other half of the participants lifted the left finger for when an object–verb pair was compatible, whereas they lifted the right finger when a pair was incompatible.

TABLE 1 | Combinations of words and objects.

Verbs Objects	Manual action	Manual action (incompatible)	Non-manual action	Non-manual action (incompatible)
Ball	投げる (throw)	そそぐ (pour)	飛ぶ (fly)	折れる (snap)
Bottle	そそぐ (pour)	焼く (cook)	割れる (break[a])	焦げる (burn)
Can	持つ (hold)	掘る (dig)	倒れる (fall)	鳴る (sound)
Hammer	たたく (hit)	書く (write)	落ちる (fall)	焦げる (burn)
Knife	切る (cut)	たたく (hit)	刺さる (stick)	回る (twist)
Mug cup	飲む (drink)	刺す (stab)	割れる (break[a])	飛ぶ (fly)
Frying pan	焼く (cook)	投げる (throw)	焦げる (burn)	刺さる (stick)
Pen	書く (write)	飲む (drink)	落ちる (fall)	ぶつかる (clash)
Mobile phone	持つ (hold)	飲む (drink)	鳴る (sound)	刺さる (stick)
Tambourine	たたく (hit)	そそぐ (pour)	鳴る (sound)	滑る (slip)

[a] *In English "Break" can be both transitive/intransitive verbs. However, in Japanese different verbs are used as a transitive verb (割る,"waru") and as an intransitive verb (割れる,"wareru"). Therefore, Japanese participants surely recognize that the word "割れる(wareru)" is an intransitive verb.*

The objects are all typically operated with a single hand. English translations of the verbs re written underneath each kanji.

Results

The mean CRT (for correct responses only) under each experimental condition is shown in **Table 2**. The results of three-way ANOVAs for all factors are reported in **Table 3**. Incorrect responses (4.1% of total trials) were excluded from the statistical analysis. The main effect of hand position was significant. The CRT was significantly faster under the normal hand position than under the constrained hand position. The main effect of compatibility was significant. The CRT was significantly faster when the object–verb combination was compatible than when it was incompatible. The main effect of verb type was significant. The CRT was significantly faster for MA verbs than for non-MA verbs. Contrary to our expectation, the interaction between verb type and hand position was not significant. The interaction between compatibility and hand position was significant. Follow-up, multiple pairwise comparisons showed that the CRTs were significantly different between each pair of four conditions (i.e., two compatibilities × hand positions). The interaction between compatibility and verb type was also significant (see **Figure 3**). Because the most interesting contrast was observed between the compatible and incompatible combinations, multiple pairwise corrections with Bonferroni corrections were made only to statistically test the contrast. When the object–verb combination was compatible, the CRT was significantly faster for MA verbs than for the non-MA verbs.

The mean error rate under each experimental condition is shown in **Table 2**. An ANOVA for the error rate showed that only the main effect of verb type was significant (see **Table 3**). Significantly fewer errors were found when MA verbs were presented than when non-MA verbs were presented. Neither the main effects of compatibility and hand position nor the interaction between these three factors was significant.

The mean SRT under each experimental condition is shown in **Table 2**. Outliers (3 × SD ± mean) were excluded from the statistical analyses. An ANOVA for the SRT showed no significant main effects or interactions.

The results of two-way ANOVA (task type × hand position) showed that the main effect of the task type was significant [$F_{(1,\ 17)} = 688.0$, $p < 0.001$, $\eta_{\mathrm{p}}{}^2 = 0.97$]. The reaction time was significantly slower for the CRT than for the SRT. The interaction between task type and hand position was significant [$F_{(1,\ 17)} = 11.66$, $p < 0.005$, $\eta_p{}^2 = 0.41$]. When the task was a compatibility judgment, the reaction time was significantly faster under the normal hand position than under the constrained hand position. In contrast, when the task was a word detection, there was no significant difference in reaction time between the two tasks.

Discussion

The results of the compatibility judgment task showed that, contrary to our expectation, the interaction between verb type and hand position was not significant. Instead, under the constrained condition, the CRTs became slower for both MA and non-MA verbs. We hypothesized that responding with a constrained arm posture would only affect the tasks with MA verbs because only these verbs are related to manual actions. However, the results suggest that the response was delayed regardless of whether the verbs involved manual actions. To address the reliability of the results, we investigated whether they could be replicated in the same procedure with a different response method.

Performance on the word detection task did not change even when the arm was constrained. In other words, constraining arm posture led to delayed responding only in the CRT task, but not the SRT task. This suggests that the delayed response induced by constrained arm posture in the compatibility judgment task was not merely due to the difficulty of responding via button when the arm was constrained (i.e., basic motor interference). The CRTs were slower for non-MA verbs than for MA verbs; moreover, the error rate was higher for non-MA verbs. These findings showed the difficulty in selecting the correct response for non-MA verbs.

EXPERIMENT 2

There were two major purposes of Experiment 2. First, we investigated whether the unexpected results obtained in Experiment 1 would be replicated even with the change in response method. As stated, contrary to our expectations, constrained arm posture led to a delayed reaction time not only

FIGURE 2 | The two hand position conditions. Left panel: normal position, **Right panel**: constrained position.

with MA verbs but also with non-MA verbs. We addressed whether these results were reliable. Secondly, we addressed whether the results in Experiment 1, a delay in the compatibility judgment task as a result of constrained arm posture, were not simply due to the difficulty of responding with the index fingers when the arms were constrained. For this purpose, the same tasks as those in Experiment 1 were performed with a change in the response method from a finger response to a vocal response.

Methods

Eighteen right-handed, young Japanese individuals participated (nine females and nine males, mean age = 29.2, *SD* = 5.7). Written, informed consent was obtained from each participant prior to the experiment. The protocol was approved by the ethics committee at the Tokyo Metropolitan University in accordance with the Declaration of Helsinki (authorization number H27-15). Responses were measured from voice onset time. For the compatibility judgment task, participants were asked to say "compatible" in Japanese ("Au") or "incompatible" in Japanese ("Awanai"). In the word detection task, half of participants responded by saying "Au" for the former half of the trials, whereas they responded with "Awanai" for the latter half of the trials.

Results and Discussion

The mean CRT (for correct responses only) under each experimental condition is shown in **Table 2**. Incorrect responses (2.1% of total trials) were excluded from the statistical analysis. The results of three-way ANOVAs for all factors are reported in **Table 3**. The main effect of hand position was significant. The CRT was significantly faster under the normal hand position than under the constrained hand position. The main effect of compatibility was significant. The CRT was significantly faster when the object–verb combination was compatible than when it was incompatible. The main effect of verb type was significant. The CRT was significantly faster for MA verbs than for non-MA verbs. The interaction between compatibility and verb type was also significant (see **Figure 4**). Because the most interesting contrast was observed between the compatible and incompatible combinations, multiple pairwise corrections with Bonferroni corrections were made only to statistically test the contrast. When the object–verb combination was compatible, the CRT was significantly faster for MA verbs than for the non-MA verbs. The interaction between verb type and hand position was not significant.

The mean error rate under each experimental condition is shown in **Table 2**. An ANOVA for the error rate showed that only the main effect of verb type was significant. Significantly fewer errors were found when MA verbs were presented than when non-MA verbs were presented. Neither the main effects of compatibility and hand position nor the interaction between these three factors was significant. The mean SRT under each experimental condition is shown in **Table 2**. Outliers (3 × SD ± mean) were excluded from the statistical analyses. An ANOVA for the SRT showed no significant main effects or interactions.

The results of the two-way ANOVA (task type × hand position) showed that the main effect of the task type was significant [$F_{(1,\,17)} = 350.08, p < 0.001, \eta_p{}^2 = 0.95$]. The reaction time was significantly slower for the CRT than for the SRT. The interaction between task type and hand position was significant [$F_{(1,\,17)} = 5.79$, $p < 0.05$, $\eta_p{}^2 = 0.25$]. When the task was a compatibility judgment, the reaction time was significantly faster under the normal hand position than under the constrained hand position. In contrast, when the task was a word detection, there was no significant difference in reaction time between the two tasks.

The results of Experiment 2 mostly replicated the results of Experiment 1. Most importantly, the results of the compatibility judgment task failed to show a significant interaction between hand position and verb type. Instead, a main effect of hand position was found; under the constrained arm posture condition, the CRTs became slower for both MA and non-MA verbs. The results also replicated the findings in Experiment 1 in that (a) the compatibility judgment task was slower overall for non-MA verbs than for MA verbs; (b) the compatibility judgment task had overall slower RTs for incompatible pairs than for compatible pairs; and (c) the error rate was higher for non-MA verbs than for MA verbs. These findings showed the reliability of the findings in Experiment 1.

In Experiment 2 we changed the response method from a response by finger to a vocal response. Nevertheless, the results of Experiment 2 mostly replicated the results of Experiment 1. These findings suggest that the delayed response selection did

TABLE 2 | Mean choice reaction time (CRT), Error rate, and simple reaction time (SRT) in Experiment 1 ∼ 3.

Verb-Object Compatibility	Compatible				Incompatible			
Verb type	**MA**		**Non-MA**		**MA**		**Non-MA**	
Hand position	**Unconstrained**	**Constrained**	**Unconstrained**	**Constrained**	**Unconstrained**	**Constrained**	**Unconstrained**	**Constrained**
EXP. 1								
CRT (ms)	565 ± 63	596 ± 64	604 ± 55	648 ± 75	636 ± 52	656 ± 51	639 ± 52	662 ± 58
Error rate (%)	3.1 ± 2.9	2.7 ± 2.9	4.4 ± 5.1	4.7 ± 5.1	3.8 ± 3.6	3.7 ± 2.7	6 ± 3.8	4.3 ± 3.9
SRT (ms)	323 ± 55	319 ± 41	321 ± 61	319 ± 39	328 ± 59	318 ± 41	323 ± 56	317 ± 33
EXP. 2								
CRT (ms)	645 ± 83	669 ± 91	686 ± 80	711 ± 87	707 ± 76	727 ± 79	707 ± 79	724 ± 83
Error rate (%)	1 ± 1.4	1.7 ± 2.7	2.7 ± 4.1	2.7 ± 3.9	1.7 ± 2.9	1.3 ± 2.1	2.7 ± 5.1	2.9 ± 4.3
SRT (ms)	379 ± 79	380 ± 85	378 ± 82	374 ± 85	381 ± 78	377 ± 83	380 ± 82	375 ± 86
EXP. 3								
CRT (ms)	480 ± 56	530 ± 84	516 ± 58	554 ± 102	534 ± 46	567 ± 80	556 ± 52	589 ± 87
Error rate (%)	2.9 ± 3.1	2.3 ± 2.8	5.5 ± 5.5	5.2 ± 3.5	1.8 ± 2.9	1.9 ± 2.5	2.2 ± 3.5	3.3 ± 3.7
SRT (ms)	316 ± 64	321 ± 52	316 ± 64	313 ± 55	316 ± 65	315 ± 59	315 ± 67	315 ± 55

Standard deviations added.

not simply originate from the difficulty of responding with the constrained arm.

EXPERIMENT 3

Before concluding that we did not find the evidence that restriction of arm movements only affects processing of MA verbs, an additional experiment was planned to exclude the possibility that the results, as obtained in Experiments 1 and 2, were produced merely due to the experimental condition in which a pictured stimulus of an object was presented before a verb. Gallivan et al. (2009) showed that, even when participants were asked to merely observe an object, brain areas related to motor planning and action were activated. Assuming that the same brain activity was triggered by the presentation of a pictured object stimulus in our experiments, it is possible that constrained arm posture led to delayed judgment because the information processing of a manipulable object, rather than a verb, was affected. To exclude this possibility, we conducted an experiment in which the protocol was the same as in Experiment 1, but the order of presenting the object and verb was reversed.

Methods

Eighteen right-handed, young Japanese individuals participated (twelve females and six males, mean age = 23.9, *SD* = 5.7). Written, informed consent was obtained from each participant prior to the experiment. The protocol was approved by the ethics committee at the Tokyo Metropolitan University in accordance with the Declaration of Helsinki (authorization number H27-15). The protocol was the same as in Experiment 1, with the exception that the order of presenting an object and verb was reversed (see **Figure 1B**). That is, now the verb was presented before the picture, and subjects again had to judge whether the verb–picture pairs were compatible or incompatible.

Results and Discussion

The mean CRT (for correct responses only) under each experimental condition is shown in **Table 2**. Incorrect responses (4% of total trials) were excluded from the statistical analysis. The main effect of compatibility was significant. The CRT was significantly faster when the object–verb combination was compatible than when it was incompatible. The main effect of hand position was significant. The CRT was significantly faster under the normal hand position than under the constrained hand position. The main effect of verb type was significant. The CRT was significantly faster for the MA verb than for the non-MA verb. The interaction between verb type and hand position was not significant.

The mean error rate under each experimental condition is shown in **Table 2**. Significantly fewer errors were found when MA verbs were presented than when non-MA verbs were presented. A significant interaction between compatibility and verb type showed that, when the object–verb combination was compatible, the error rate was significantly lower for the MA verb than for the non-MA verb. For non-MA verbs, the error rate was significantly lower when the object–verb combination was incompatible than when it was compatible. The mean SRT under each experimental condition is shown in **Table 2**. Outliers (3 × SD ± mean) were excluded from the statistical analyses. An ANOVA for the SRT showed no significant main effects or interactions.

The results of two-way ANOVAs (task type × hand position) showed that the main effect of the task type was significant [$F_{(1, 17)} = 152.23$, $p < 0.001$, $\eta_p{}^2 = 0.89$]. The reaction time was significantly slower for the CRT than for the SRT. The main effect of hand position was significant [$F_{(1, 17)} = 8.15$, $p < 0.05$, $\eta_p{}^2 = 0.32$]. The reaction time was significantly faster under the normal hand position than under the constrained hand position. The interaction between task type and hand position was significant [$F_{(1, 17)} = 9.11$, $p < 0.01$, $\eta_p{}^2 = 0.35$]. When the task was a compatibility judgment, the reaction time was significantly faster

TABLE 3 | Three-way (compatibility, verb type, and hand position) analysis of variance (ANOVA) on all factors in all experiments.

	CRT				Error rate			SRT		
	Dfs	***F***	***P***	η_p^2	***F***	***P***	η_p^2	***F***	***P***	η_p^2
Exp. 1 compatibility (C)	1, 17	29.58	< 0.001	0.63	0.67	0.42	0.04	0.81	0.38	0.04
verb type (V)	1, 17	44.33	< 0.001	0.72	6.12	< 0.05	0.27	1.36	0.26	0.07
hand position (H)	1, 17	16.44	< 0.001	0.49	1.16	0.29	0.06	0.37	0.55	0.02
C × V	1, 17	23.87	< 0.001	0.58	0.04	0.84	0.002	0.38	0.55	0.02
C × H	1, 17	4.55	< 0.05	0.21	1.08	0.31	0.06	2.28	0.15	0.12
V × H	1, 17	0.98	0.34	0.05	0.34	0.57	0.02	0.29	0.59	0.02
C × V × H	1, 17	0.64	0.44	0.03	2.70	0.12	0.13	0.12	0.73	0.01
Exp. 2 compatibility (C)	1, 17	29.71	< 0.001	0.63	0.01	0.92	0.001	0.16	0.69	0.01
verb type (V)	1, 17	40.16	< 0.001	0.70	5.06	< 0.05	0.23	2.45	0.14	0.12
hand position (H)	1, 17	6.87	< 0.05	0.29	0.28	0.6	0.02	0.21	0.65	0.01
C × V	1, 17	35.08	< 0.001	0.67	0.001	0.97	0.000	0.34	0.57	0.02
C × H	1, 17	2.14	0.16	0.11	0.36	0.56	0.02	0.67	0.42	0.03
V × H	1, 17	0.18	0.67	0.01	0.06	0.81	0.003	1.39	0.25	0.07
C × V × H	1, 17	0.41	0.53	0.02	0.88	0.36	0.04	0.23	0.64	0.01
Exp.3 compatibility (C)	1, 17	21.47	< 0.001	0.56	4.05	0.06	0.19	0.66	0.43	0.04
verb type (V)	1, 17	27.99	< 0.001	0.62	17.84	< 0.001	0.51	2.55	0.13	0.13
hand position (H)	1, 17	11.01	< 0.005	0.39	0.03	0.87	0.001	0.01	0.94	0.00
C × V	1, 17	1.14	0.30	0.06	5.34	< 0.05	0.24	2.31	0.15	0.12
C × H	1, 17	2.52	0.13	0.13	1.36	0.26	0.07	0.22	0.64	0.01
V × H	1, 17	0.71	0.41	0.04	0.63	0.44	0.03	1.45	0.24	0.07
C × V × H	1, 17	1.80	0.19	0.09	0.43	0.52	0.02	1.89	0.18	0.10

under the normal hand position than under the constrained hand position. In contrast, when the task was a word detection, there was no significant difference in reaction time between the two tasks.

The results of Experiment 3 replicated the findings in Experiments 1 and 2 in that the CRTs became slower with constrained arm posture not only for MA verbs but also for non-MA verbs. With this finding, we excluded the possibility that this result was produced merely due to an experimental condition in which a pictured object stimulus was presented before a verb.

Considering that Japanese is an SOV language (i.e., subject, object, and verb within a sentence typically appear in that order), the verb and object pair was presented in a non-canonical order (i.e., a verb was presented before an object). Considering this fact, one might expect that the compatibility judgment task became slower in Experiment 3 than in Experiments 1 and 2. Interestingly, however, the CRT was faster in Experiment 3 than in Experiments 1 and 2. This suggests that the presentation of the verb and object pair in a non-canonical order did not impair judgment. The results also replicated the findings in Experiments 1 and 2 in that the error rate was higher for non-MA verbs than for MA verbs. In addition, when the object–verb combination was compatible, the non-MA verb had the highest rate of failure in Experiment 3. These findings showed the reliability of the findings in our study.

The results in Experiment 3 showed that, when the object-verb combination was compatible, the error rate was significantly lower for the MA verb than for the non-MA verb. Because this was not the case in Experiments 1 and 2, the results seemed to be related to the change in the protocol in Experiment 3 that a verb was presented before an object. Unfortunately, however, we have no reasonable explanation for why such a result was produced with this protocol.

GENERAL DISCUSSION

The present study investigated whether constrained arm posture would result in a delay in the CRTs necessary for the processing of verbs referring to arm actions. We hypothesized that responding with a constrained arm posture would only affect task performances with MA verbs, because only these verbs are related to manual actions. However, the results obtained from three experiments showed that the response was delayed regardless of whether the verbs involved manual actions.

The results obtained from three experiments showed that (a) delayed CRTs with constrained arm posture in the compatibility judgment task were observed when participants reacted with their hands (Experiments 1 and 3) or their voice (Experiment 2); (b) constrained arm posture had no effects on SRTs; and (c) throughout all experiments, constraining arm posture induced slower responses, but only in the CRT task and not the SRT task. These results suggest that the results regarding delayed CRTs were not merely due to the difficulty of operating a

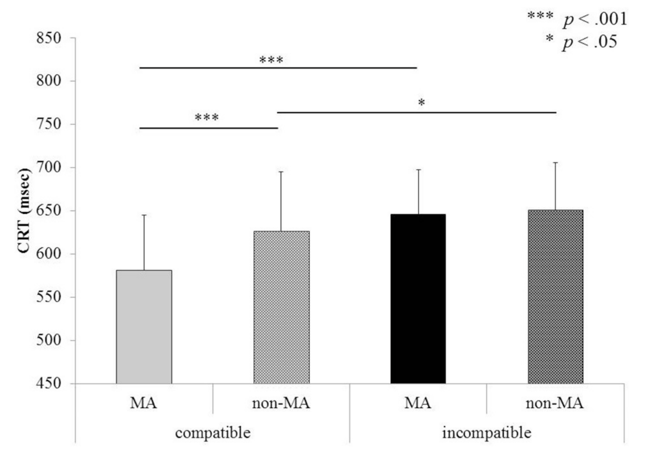

FIGURE 3 | Mean CRT for compatible and incompatible pairs, separately for the MA (manual action) and non-MA verb types in Experiment 1.

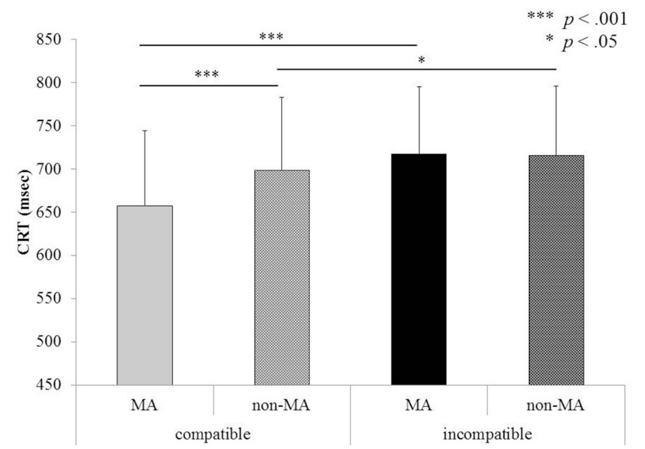

FIGURE 4 | Mean CRT for compatible and incompatible pairs, separately for the MA and non-MA verb types in Experiment 2.

response button when the arm was constrained (i.e., basic motor interference).

Constrained arm posture resulted in delayed CRTs regardless of the "manipulability" as symbolized by the verbs. This was different from our hypothesis that delayed CRTs with constrained arm posture would be observed only with MA verbs. This hypothesis was based on previous studies, demonstrating that the brain areas for action planning and execution are involved in the information processing of action-related words (Hauk et al., 2004; Tettamanti et al., 2005; Aziz-Zadeh et al., 2006; Péran et al., 2009; Raposo et al., 2009) but not likely in the processing of non-action-related verbs. It could be the case that (a subset of) the non-MA verbs was still associated with manual activities. For example, we had selected the verbs *fall* and *sound* as non-MA verbs, with the noun *can*. But one could also envisage a scenario whereby a falling can (plus the resulting sound) were caused may manual action, e.g., throwing or dropping. After we had conducted this experiment we obtained semantic ratings of the object-verb pairs used in Experiments 1–2. Fifteen young Japanese individuals participated (five females and ten males, mean age = 30.8, *SD* = 5.9, 10 of them had participated in Experiments 1–2) and they rated on a 5-point scale to what extent each object-verb pair would be considered a manual-action (MA)-related (0: not MA-related at all, 5: strongly MA-related). The mean and SD are shown as the Supplementary Data. Clearly, the results showed that our MA verbs were rated much higher as manual actions than our non-MA verbs, which suggests that our choice of stimulus material was adequate.

A second possible explanation for our findings could be that regardless of the verb type, information processing of all verbs takes place in the motor system. Yokoyama et al. (2006) indicated that the brain areas activated while participants read active verbs (e.g., *call*), passive verbs (e.g., *called*), and nouns showed comparable activation patterns. In their study, the activated brain areas included the bilateral inferior frontal cortex, occipital, the left middle, and inferior temporal cortices. Siri et al. (2008) also showed that action nouns (e.g., *the eating*) and verbs (infinitive verbs, e.g., *to eat*, and inflected verbs, e.g., *she/he eats*) are processed by a common neural system. Considering these previous findings, our results may have shown that the information processing of general verbs takes place in the motor system regardless of whether the verbs are related to action involving manipulation of an object. Because only verbal material was used in the present study, we could not exclude the possibility that all language processing is delayed. Future studies are necessary to address whether constraining arm posture would affect processing of action verbs but not of other types of verbs.

A third explanation is that there could be motor interference, e.g., a greater level of motor activity, which interferes with response choice when one out of two possible responses has to be selected. Based on the results obtained from the word detection task (i.e., measurement of the SRT), we excluded the possibility that delayed judgment was not simply due to the difficulty of responding with the hand (i.e., very basic motor interference). However, the choice reaction time task are not only cognitively but also motorically more complex than the simple reaction time task, because there are two available motor responses. Future studies are necessary to investigate the impact of more complex motor interference.

A final explanation could be that the motor system is only weakly coupled to semantic processing. The literature to date is in fact mixed. For example, in the field of Parkinson's disease it has been suggested that this motor disorder could lead to delayed processing of action verbs, based on the idea that mental simulation (and hence comprehension) of certain activities would be compromised in this patient group. However, some authors (e.g., Fernandino et al., 2013) found evidence for delayed action verb processing, whereas others (e.g., Kemmerer et al., 2013) found no such effect. Thus, embodiment effects are not consistently found in the literature and may be weak.

In our study, participants judged the compatibility of an object and a verb. Although the results obtained with the incompatible conditions were not directly relevant to answer our main theoretical question, these results were necessary for more practical reasons. The compatibility manipulation served one important purpose that is crucial to the experiment; namely, it forced participants to engage in deep semantic processing of the verb–object pair, thereby preventing shallow processing and keeping alertness to the stimuli high. The fact that incompatible pairs had slower CRTs than compatible pairs, which result was obtained consistently across all experiments, underscores that participants paid full attention to the verbs, so that embodied language effects (due to arm constraint) could potentially be elicited.

We would like to acknowledge several limitations to our study. First, we noticed substantial RT differences across the various object-verb pairs, for which we have no ready explanation. This source of variance may have obscured embodiment effects. Second, it could be that repetition effects (each object-verb pair was shown 5 times) were present, potentially masking relevant effects. Third, it could be that the temporary restraint of the arm was simply too brief to affect the motor representations. Future studies could manipulate the duration (>24 h) of limb immobilization and test whether this leads to a gradual change in action processing of verbs.

Despite these caveats, we believe our data can add to the debate as to whether peripheral body states can influence verb processing, and provide suggestions for fruitful innovative experiments.

AUTHOR CONTRIBUTIONS

MY designed and conducted all of three experiments, and write the manuscript. JS supported writing introduction of the manuscript, particularly in terms of embodied cognition, and helped planning our experimental paradigm. TH supervised this study and direct the construction of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2017.00057/full#supplementary-material

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Act on Numbers: Numerical Magnitude Influences Selection and Kinematics of Finger Movement

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In the past decade hand kinematics has been reliably adopted for investigating cognitive processes and disentangling debated topics. One of the most controversial issues in numerical cognition literature regards the origin – cultural vs. genetically driven – of the mental number line (MNL), oriented from left (small numbers) to right (large numbers). To date, the majority of studies have investigated this effect by means of response times, whereas studies considering more culturally unbiased measures such as kinematic parameters are rare. Here, we present a new paradigm that combines a "free response" task with the kinematic analysis of movement. Participants were seated in front of two little soccer goals placed on a table, one on the left and one on the right side. They were presented with left- or right-directed arrows and they were instructed to kick a small ball with their right index toward the goal indicated by the arrow. In a few test trials participants were presented also with a small (2) or a large (8) number, and they were allowed to choose the kicking direction. Participants performed more left responses with the small number and more right responses with the large number. The whole kicking movement was segmented in two temporal phases in order to make a hand kinematics' fine-grained analysis. The Kick Preparation and Kick Finalization phases were selected on the basis of peak trajectory deviation from the virtual midline between the two goals. Results show an effect of both small and large numbers on action execution timing. Participants were faster to finalize the action when responding to small numbers toward the left and to large number toward the right. Here, we provide the first experimental demonstration which highlights how numerical processing affects action execution in a new and not-overlearned context. The employment of this innovative and unbiased paradigm will permit to disentangle the role of nature and culture in shaping the direction of MNL and the role of finger in the acquisition of numerical skills. Last but not least, similar paradigms will allow to determine how cognition can influence action execution.

Keywords: kinematics, action planning, action execution, mental number line, SNARC effect

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INTRODUCTION

Humans usually represent numbers on a mental number line (MNL), oriented from left-to-right. Along the MNL, small numbers are placed on the left side and large numbers on the right side of space (Dehaene, 2011). The seminal experimental demonstration of the left-to-right oriented MNL, which has been extensively replicated over time, is the SNARC effect (spatial-numerical association of response codes; Dehaene et al., 1993). This effect shows that adult humans are faster in responding to small numbers on the left side of space, and in responding to large numbers on the right side of space. More recently, it has been assumed the existence of multiple spatial mappings which comprises an association between number and vertical space, as well as an association between number and near/far space (Winter et al., 2015).

Up to now, a large body of literature has replicated the evidence that number processing can modulate response times, but few studies investigated whether number processing could affect the selection of the responses. The first attempt to study this facet of the SNARC was conducted by Daar and Pratt (2008), using a free-response task. They presented participants with a stimulus, which could be a number (either a small or a large one) or a neutral character, on the central part of a monitor. Participant were required to press either a left or a right button on a keyboard (free choice task) as soon as the stimulus turned from white to green. When participants responded to small numbers they performed more left-key presses. Similarly, in responding to large numbers, they produced more right key-presses. This shows that numerical magnitude not only affects the response's speed (as previously demonstrated in other researches) but also the direction of the choice. This evidence suggests that the spatial representation of numerical magnitude could influence which of two responses is selected for action (Daar and Pratt, 2008). The "free response" task used by Daar and Pratt (2008) differs from the "forced-choice" tasks previously and largely used to study spatial-numerical association. In these kind of tasks, indeed, participants were forced to emit a lateral response, usually to press a left- or a right-side key. In a classical "forced-choice" task, a group of participants are for example required to press a key on the left to indicate whether a number is even and a right key when it is odd, while complementary instructions are given to a second group of participants. Interestingly, even if participants are not required to estimate numerical magnitude, responses to small numbers are faster on the left side and responses to large numbers are faster on the right side of the space: SNARC effect (Dehaene, 2011). Conversely, a "free response" task allows to investigate what response is spontaneously selected. Moreover, adopting kinematic measures instead of response times provides a more fine-tuned analysis of movement, a larger range of degrees of freedom and a more sensitive investigation. In fact, a growing number of studies are now using motion capture and detailed kinematic analyses to parameterize behavior and to deeply examine questions relating to cognitive processing in naturalistic protocols (for reviews, see Castiello, 2005; Krishnan-Barman et al., 2017). From this fascinating perspective, an essential improvement of the actual knowledge would be obtained by combining a "free response" task with a kinematic analysis of movement, which may allow to understand how the responses are executed (Rugani and Sartori, 2016). In fact, given that cognitive representations of perceptual and semantic information cannot be fully understood without considering their impact on actions (Gallese and Lakoff, 2005), the existing knowledge on MNL will be advantaged by studies that analyze the motor action while responding to a number.

Semantic information related to magnitude influences indeed movement kinematics, as shown by a few studies. In a reach-to-grasp study, participants were instructed to grasp one of two identical objects, which differed solely by a word (i.e., "large" or "small") labeled on them. Grip aperture varied accordingly with the dimension indicated by the word: it was larger for the large-labeled object and smaller for the small-labeled object (Gentilucci et al., 2000, but see also Glover and Dixon, 2002; Glover et al., 2004). Up to now, only a couple of studies has investigated the functional connection between numerical cognition and action planning (for a review see Gianelli and Fischer, 2016). Lindemann et al. (2007) asked participants to emit an odd/even judgment on Arabic digits, by grasping either a small or a large object, which required respectively a precision or a power grip. In response to small numbers precision grip movements began faster, and power grips began faster in response to large numbers. The impact of numerical magnitude on both response times and grip kinematics suggests that representations of number and representations of action share codes within a common magnitude representation's system (Lindemann et al., 2007). In another study Gianelli et al. (2012) presented participants with a digit (from 1 to 9 without 5) and asked them to grasp a small cube and to change its position before verbally judging whether the presented number was smaller or larger than 5. Both the grip aperture and the spatial dislocation of the cube were modulated by the number magnitude, showing that the processing of magnitude is strictly related to the mechanisms underlying spatial orienting and action execution (Gianelli et al., 2012). Nevertheless, this effect, as well as the data by Daar and Pratt (2008), could also reflect a highly overlearned motor association between numerical magnitudes and manual responses, which allows to perform very efficient actions in everyday life (Schwarz and Keus, 2004). It is indeed well-known that context can influence the SNARC. When adult humans are required to relate numbers to locations on a ruler, they show a classical (left-to-right) SNARC effect. But when they are required to relate numbers on a clock face, they show an inverted (right-to left) SNARC effect (Bächtold et al., 1998). In everyday life, we often perceive and act on spatially organized numbers: rulers, keyboards, and objects ordered by their dimensions by different labels (e.g., small, medium large) or Arabic digits (1, 2, 3, 4) to indicate their sizes, are clear examples of this bias. These frequent experiences could induce us to respond to small numbers with the left hand and to larger number with the right one, as well as to prepare a smaller grasping action in relation to smaller digits (Rugani and Sartori, 2016).

Here, we aimed to investigate the association between numbers and space, combining a "free response" task with the kinematic analysis of movement, in order to understand whether number processing can influence action selection and action execution. Participants wore a miniaturized soccer shoe and kicked a small ball with their right index finger. This specific type of action has recently been adopted to elicit cognitive processing and action planning (Betti et al., 2015). In the present study, participants were instructed to kick the ball toward one of two identical little soccer goals, one located on their left and the other on their right, as soon as a stimulus was presented on a monitor screen. We designed this new and unusual task to limit the influence of learned associations between numbers and motor behavior. On 60% of the trials, the stimulus consisted of a left- or right-directed arrow and participants were instructed to kick the ball toward the direction indicated by the arrow, as fast as they could. On 40% of the trials – intermixed with arrows presentation – was instead presented a numerical stimulus that could be a small (2) or a large (8) numerical stimulus. In order to compare the effect of symbolic (i.e., abstract representations of numerical magnitudes; Vogel et al., 2015) and non-symbolic numbers (i.e., when the numerical magnitude can be extrapolated from an array of elements; Feigenson et al., 2004), in 20% of the trials participants were presented with numerals (2 or 8 digit) and the remaining 20% of the trials participants were presented with arrays composed of 2 or 8 dots. In both cases participants were free to choose toward which direction to kick the ball. The first aim of the study is to investigate what action will be selected by participants in response to a numerical value. Based on previous literature (Daar and Pratt, 2008), we expect that a small number will bias the response toward the left (i.e., the ball will be kicked more often toward the left soccer door than toward the right one) and that a large number will bias the response toward the right (i.e., the ball will be kicked more often toward the right soccer door than toward the left one). The second aim of the study is to investigate the functional connection between numerical cognition and action planning. Based on previous findings by Lindemann et al. (2007), we predict that a small number will facilitate the responses on the left side and *vice versa* that large numbers will facilitate responses on the right side (e.g., reduced action duration before contact on the target).

MATERIALS AND METHODS

Participants

Nineteen students (13 males and 6 females, mean age = 22.89 years, *SD* = 2.38) took part in the experiment. All participants were right handed, had normal or corrected-to-normal vision, and were naive about the purpose of the experiment. Participants gave their written consent before the experiment. The experimental procedures were approved by the Ethics Committee of the University of Padova and were carried out in accordance with the principles of the 1964 Declaration of Helsinki.

Experimental Stimuli and Stimuli Presentation

Stimuli consisted in: (i) direction indicators: a left arrow (<) and a right arrow (>); (ii) symbolic numbers: a small digit (2, hereafter labeled as S2) and a large digit (8, hereafter labeled as S8); (iii) non-symbolic numbers: an array composed of two elements (hereafter labeled as NS2) and an array composed of eight elements (hereafter labeled as NS8; see **Figure 1**). For the non-symbolic numbers, the elements consisted in black dots of 1 cm in diameter. In the two-element array, the dots were vertically aligned and separated by a distance of 2 cm. In the eight-element array the dots were arranged in circle (circle's diameter was of 10.5 cm and elements were located 3 cm away one another). Both dispositions of the elements in the arrays were selected in order to avoid any explicit indication of direction. Arrows and digits were in Arial font, black color and 160 size. On each trial, a black fixation cross (7.5 cm by 7.5 cm, in Arial font, black color) appeared. After a 1000 ms delay, the fixation cross was replaced with a single stimulus.

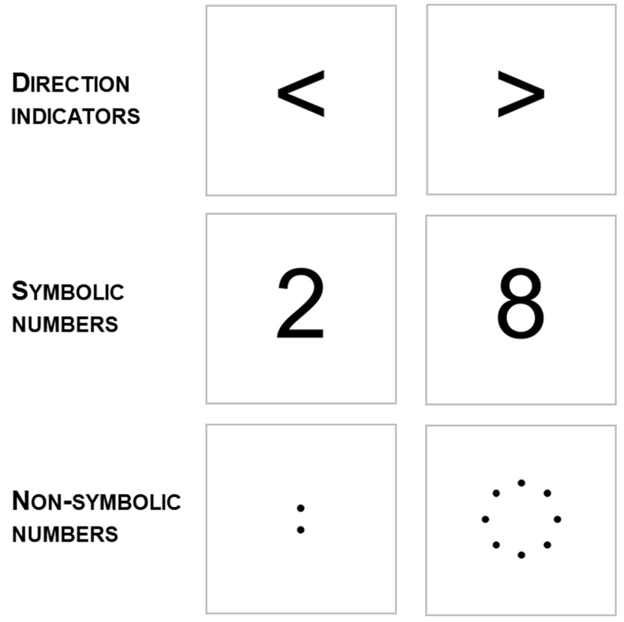

FIGURE 1 | Three stimulus types were adopted in the Experiment. Direction indicators (i.e., a left and a right arrow); symbolic numbers (i.e., a small and a large digit); non-symbolic numbers (i.e., an array composed of two elements and an array of eight elements).

Apparatus and Experimental Procedure

Participants sat on a chair in front of a table (90 cm × 90 cm) with the left wrist resting on their left leg and the right hand located in the designated start position. The experimental apparatus consisted in a work plan (93.5 cm × 74 cm) covered by a green velvet cloth. Participants' right index was introduced in a plastic sock (4.5 cm high, 2.5 cm internal diameter) of a small plastic soccer shoe (the dimensions of the sole of the shoe were: 3 cm long, 1.5 cm wide), for a schematic representation of the apparatus see **Figure 2D**. At the beginning of each trial, participants were instructed to position the sole of the shoe on a light blue footprint (3 cm long, 1.5 cm wide), depicted on the velvet cloth, located on the midline. A plastic ball (2.3 cm of diameter) was positioned on a circle plastic support (diameter of 1.5 cm) located at 0.2 cm away from the footprint. In the start position, participants were required to rest their right wrist on a support (a pillow which was 16 cm long, 11 cm wide and 6.5 cm high), which was shaped to guarantee a comfortable and repeatable posture of the right participants' hand, allowing them to equally and easily kick the ball either toward the left or the right.

Two small soccer goals (18 cm long 16 cm high; see **Figure 2A**) were located 50 cm away from the footprint, separated from each

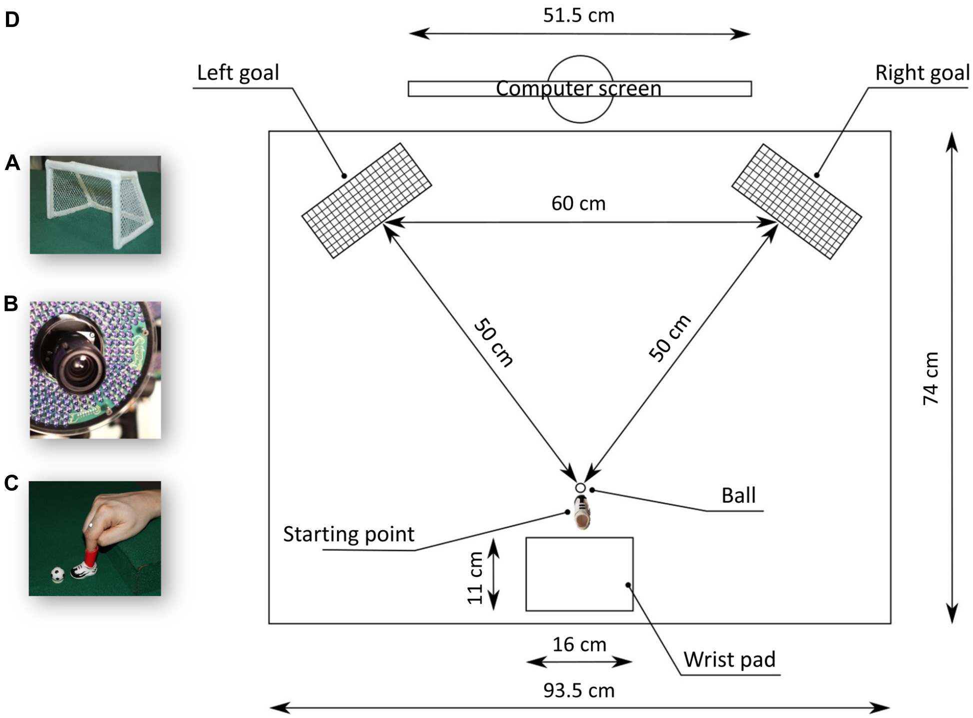

FIGURE 2 | Set up and stimuli. Two soccer doors **(A)** were disposed laterally with respect to the participant's position. A 3D-Optoelectronic SMART-D system was used to track the kinematics of the participant's right upper limb by means of six video cameras **(B)**. An infrared reflective markers was taped to the participant's index finger **(C)**. Participants sat in front of a monitor wearing a small soccer shoe positioned on a footprint, in front of a plastic ball **(D)**.

other by a distance of 60 cm and rotated by 30° with regard to the horizontal axis (see **Figure 2D**). A 24′′ monitor (resolution 1920 × 1080 pixels, refresh frequency 120 Hz) set at eye level (the eye-screen distance was 80 cm) was used to present the experimental stimuli. Participants underwent two experimental sessions (i.e., Training and Testing) and were instructed to kick the ball toward a soccer goal as soon as a stimulus appeared, at their own pace. During training trials ($N = 20$) participants kicked the ball in the direction indicated by an arrow ($N = 10$ pointing leftward and $N = 10$ rightward, presented in random order). The aim of this session was to get the participants acquainted in kicking the ball in both directions. During test trials ($N = 100$) participants were required to kick toward the direction indicated by the arrow in the 60% of the trials. They were instead free to choose the kicking direction upon presentation of symbolic and non-symbolic numbers only in the 40% of the trials in order to maintain the free-response a sporadic event and to avoid the adoption of fixed response strategies.

Arrows, digits and array of elements were intermixed in a semi-random order (i.e., the same stimulus could not appear in more than two consecutive trials). Left and right arrows were presented in 30 trials each and both symbolic and non-symbolic numbers were presented in 10 trials each.

Kinematics Recording

A 3D-Optoelectronic SMART-D system (Bioengineering Technology and Systems, B|T|S|) was used to track the kinematics of the participant's right index. One light-weight infrared reflective marker (0.25 mm in diameter; B|T|S|) was taped on the index finger's proximal phalange to measure the kicking component of the action (see **Figure 2C**). A second marker was located on the midline between the two little soccer goals, at a distance of 30 cm from each of them, and at a distance of 40 cm from the footprint. This second marker allowed to compute the finger's location in relation to the midline. Six infrared video cameras (sampling rate 140 Hz), detecting the markers' positions in a 3D space, were placed in a semicircle at a distance of 1–1.2 m from the table, see **Figure 2B**. Each camera position, roll angle, zoom, focus, threshold and brightness were calibrated and adjusted to optimize marker tracking before each experimental session. Static and dynamic calibrations were then carried out. For the static calibration, a three-axes frame of five markers at known distances from each other was placed in the middle of the table. For the dynamic calibration, a three-marker wand was moved throughout the workspace of interest for 60 s. The spatial resolution of the recording system was 0.3 mm over the field of view. The standard deviation of the reconstruction error was 0.2 mm for the x, y, and z axes.

Data Processing

As concerns behavioral data, the number of right and left kicks was calculated, separately for stimulus type and magnitude (S2, S8, NS2, and NS8). Following kinematic data collection, each trial was individually checked for correct marker identification and the SMART-D Tracker software package (B|T|S|) was used to provide a 3-D reconstruction of the marker positions as a function of time. The data were then filtered using a finite impulse response linear filter (transition band = 1 Hz, sharpening variable = 2, cut-off frequency = 10 Hz; D'Amico and Ferrigno, 1990, 1992). The measurements were made along the three Cartesian axes [i.e., X (left–right), Y (up–down), and Z (anterior–posterior)]. Movement onset was defined as the time at which the tangential velocity of the finger marker crossed a threshold (5 mm/s) and remained above it for longer than 500 ms. End of movement was defined as the time at which the finger reached the maximum extension on the Y axis, after the ball was kicked. In order to specifically investigate the temporal aspects of the movement with a fine-grained analysis, we divided the whole kicking movement in two phases: Kick Preparation and Kick Finalization, computed with respect to maximum trajectory deviation. The following temporal kinematic parameters were extracted for each individual movement using a custom Protocol run in Matlab, 2014b (The 4 Math Works, Natick, MA, United States):

Movement Time (MT): the time interval between movement onset and end of movement (ms);

Time of Maximum Left Deviation (TMLD): the time at which the index trajectory was at a maximum distance toward the left from the midline (i.e., an imaginary line connecting the footprint and the central marker) (ms);

Time of Maximum Right Deviation (TMRD): the time at which the index trajectory was at a maximum distance toward the right from the midline (ms);

Kick Preparation (KP): the time interval between movement onset and maximum trajectory deviation (ms);

Kick Finalization (KF): the time interval between maximum trajectory deviation and the end of movement (ms).

In addition, each kinematic parameter was normalized with respect to movement time, so that individual differences were accounted for.

% Time of Maximum Left Deviation (%TMLD): the percentage of time at which the index trajectory was at maximum distance toward the left from the midline (%);

% Time of Maximum Right Deviation (%TMRD): the percentage of time at which the index trajectory was at maximum distance toward the right from the midline (%).

% Kick Preparation (%KP): the time interval between movement onset and maximum trajectory deviation (ms);

% Kick Finalization (%KF): the time interval between maximum trajectory deviation and the end of movement (ms).

For each participant and kinematic index, Mean and SD was calculated, separately for each stimulus type (S2, S8, NS2, NS8, <,>) and kicking direction (left, right). The first 10 trials for each arrow direction (left or right) constituted the neutral baseline given that participants neither had to process the numerical information nor decide the direction in which kicking the ball. Baseline was calculated in this way because, while responding to arrows, participants did not have to process the numerical information and they did not have to decide the direction in which kicking the ball, since it was explicitly indicated by the arrow.

Data Analysis

Behavioral Analysis

For each participant and for each trial, the means (+ SD) percentages of left kicks were computed as: (number of left choices/10) × 100. By using this formula, values of around 50% indicated no preference for kicking toward either direction; values > 50% indicated a preference for kicking toward the left; and < 50% indicated a preference for kicking toward the right. A repeated-measures ANOVA on Stimulus type (symbolic or non-symbolic) and Magnitude (small vs. large numbers) was computed on the percentage of left kicks. Significant departures from chance level (50%) were estimated by one-sample two-tailed *t*-tests.

Kinematic Analysis

The mean value for each parameter of interest and for each participant was compared with the corresponding neutral baseline (i.e., kicks performed in response to the first 10 arrows indicating the same direction). For example, kicks in which participants kicked toward the left in response to a symbolic stimulus were compared with the first 10 test trials in which participants responded to left arrows. Then, for each type of stimulus we compared, using a *t*-test, the means for each index with the relative neutral baseline. Bonferroni's correction for multiple comparisons was adopted to prevent Type-1 errors. Crucially, data concerning the two different movements (i.e., left and right kicks) were considered separately and compared to their respective baseline due to mechanical and anatomical differences.

RESULTS AND DISCUSSION

Behavioral Results

The repeated-measures ANOVA on left kicks showed a significant main effect of Stimulus type [$F_{(1,18)} = 8.16$, $p < 0.05$, $\eta^2_p = 0.31$] and Magnitude [$F_{(1,18)} = 5.89$, $p < 0.05$, $\eta^2_p = 0.25$]. Symbolic stimuli elicited more left kicks than non-symbolic stimuli. In terms of magnitude, participants chose more frequently to kick toward the left soccer door in response to a small number presentation rather than in response to a large number presentation. In particular, one-sample *t*-tests against 50% chance value revealed that, responding to a small number (S2, NS2), participants kicked the ball toward the left statistically more often than chance level [$t_{(18)} = 3.01$; $p < 0.01$]. On the contrary, in response to a large number (S8, NS8), participants kicked the ball toward the left at chance level [$t_{(18)} = 1.01$; $p = 0.32$]. Specifically, participants kicked the ball toward the left statistically more often than chance level

[$t_{(18)} = 3.73$; $p < 0.01$] for S2, but not for S8 [$t_{(18)} = 1.56$; $p = 0.13$], NS2 [$t_{(18)} = 1.73$; $p = 0.10$], or NS8 [$t_{(18)} = 0.18$; $p = 0.86$].

Kinematic Results

The fine-grained analysis of temporal phases revealed distinct patterns of movement for small and large symbolic numbers.

Symbolic Stimuli

As concerns left kicks in response to small number (S2), MT was significantly longer with respect to baseline values [437.532 vs. 418.246, respectively; $t_{(18)} = 2.606$, $p = 0.018$]. In particular, a statistically significant delay of TMRD during the Preparation Phase was noticed compared to the baseline in both absolute [235.405 vs. 197.556 ms, respectively; $t_{(18)} = 3.685$, $p = 0.002$] and relative [55 vs. 49%, respectively; $t_{(18)} = 2.302$, $p = 0.034$; see **Figure 3**] terms. A longer Preparation Phase for left kicks in response to a small number implies that a shorter Finalization Phase was then performed compared to the baseline [45 vs. 51%, respectively; $t_{(18)} = -2.302$, $p = 0.034$]. No statistically significant differences were noticed for left kicks in response to a large number (S8; all $p_s > 0.05$).

As concerns right kicks in response to large number (S8), the experimental manipulation did not affect MT compared to the baseline ($p = 0.232$), suggesting that either anatomical constraints limited the degrees of freedom during action execution, or that compensative strategies were adopted in order to maintain a constant movement duration (i.e., the Isochrony Principle; Sartori et al., 2013). However, a statistically significant delay of TMLD during the Preparation Phase was noticed compared to the baseline in both absolute [215.599 vs. 171.416 ms, respectively; $t_{(18)} = 3.119$, $p = 0.006$] and relative [54 vs. 45%, respectively; $t_{(18)} = 2.860$, $p = 0.015$; see **Figure 4**] terms. A longer Preparation Phase for right kicks in response to a large number implies that a shorter Finalization Phase was then performed compared to the baseline in both absolute [189.188 vs. 217.814 ms, respectively; $t_{(18)} = -2.608$, $p = 0.018$] and relative [46 vs. 55%, respectively; $t_{(18)} = -2.680$, $p = 0.015$] terms. No statistically significant differences were noticed for right kicks in response to a small number (S2; all $p_s > 0.05$).

Non-symbolic Stimuli

No statistically significant differences were noticed for NS2 (all $p_s > 0.05$) and NS8 (all $p_s > 0.05$), suggesting that non-symbolic stimuli did not affect kinematics.

CONCLUSION

This study focused on the investigation of the MNL from an innovative perspective. To date, the majority of studies have investigated the association between numbers and space by analyzing response times, whereas researches focused on response selection, and also on more subtle measures, such as kinematic indexes, are rare. The aim of the present research was to fill this gap in the scientific literature. We designed a new, unusual and therefore not overlearned paradigm that combines a "free response" task with a hand kinematic analysis of movement. This allowed to understand *what* responses will be selected and *how* such responses are executed. Participants seated in front of a monitor and two laterally placed little soccer goals. They were required to kick, with their right index, a small ball toward either soccer goal as soon as they were presented with a stimulus. Three types of stimuli have been used: arrows (left or right) which explicitly indicated the kicking direction; symbolic numbers (digits 2 and 8) and non-symbolic numbers (array composed of 2 or 8 elements). Both types of numerical stimuli did not explicitly indicate a direction, unless the numerical magnitude could influence the chosen direction. Behavioral results showed that

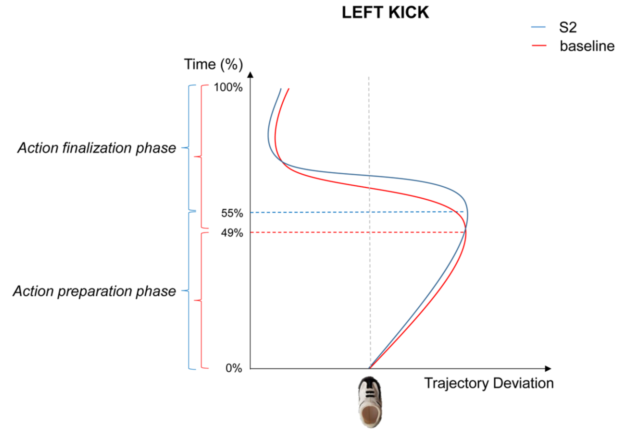

FIGURE 3 | Graphical representation of the mean trajectories for left kicks following S2 presentation (blue), and left arrows (red). During the Kick Preparation phase, trajectories are directed to the opposite side with respect to the kick direction (i.e., rightward) and show different temporal patterns across conditions.

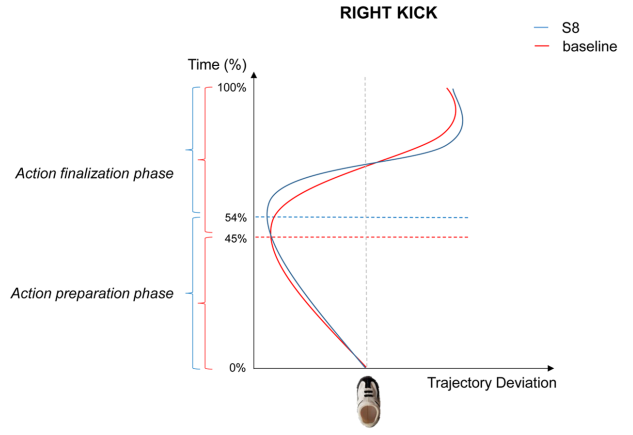

FIGURE 4 | Graphical representation of the mean trajectories for right kicks following S8 presentation (blue), and right arrows (red). During the Kick Preparation phase, trajectories are directed to the opposite side with respect to the kick direction (i.e., leftward) and show different temporal patterns across conditions.

a small symbolic number prompted participants to selectively produce more kicks directed toward the left, while this bias did not emerge in responding to non-symbolic numbers. This suggests that the spatial representation of numerical magnitude plays a role in determining which of two responses was selected for action.

More interestingly, numerical magnitude affected the execution of a same action. We analyzed the kinematic parameters of the hand action, by dividing the whole kicking movement in two parts: Kick Preparation and Kick Finalization. Kinematics analysis revealed an effect of both small and large numbers on the timing for action execution. In responding to small numbers toward the left and to large number toward the right, participants took longer in preparing the action but they were faster to finalize the action. Crucially, the same kinematic parameter (i.e., the time of maximum trajectory deviation) was influenced in a complementary fashion for small and large symbolic numbers. S2 specifically altered the temporal aspects of left kick whereas S8 specifically modified right kicks.

Our evidence is in line with previous scientific literature. In kinematic terms, we adopted a spatial trajectory measure (i.e., trajectory deviation) that has been proved to be sensitive to participant's motor intentions (Georgiou et al., 2007; Becchio et al., 2008), revealing that the motor system incorporates overarching goals into the action plan. Previous studies demonstrated that the trajectory path was increased and that the deviation anticipated for highly demanding actions with respect to simpler actions (Becchio et al., 2008; Sartori et al., 2009). Here, we found that our experimental manipulation highly influenced this measure leading to anticipated time intervals between maximum trajectory deviation and the end of movement. This seems to suggest that the processing of numerical magnitude increases executive load during Kick Preparation but then facilitates Kick Finalization. It could be argued that the sample size adopted in this study was too small. However, previous influential literature adopting the same kinematic approach recruited a similar number of participants. We are therefore quite confident that the sample size was appropriate for this methodological approach (see for example Grosjean et al., 2009; Hardwick and Edwards, 2012; Ménoret et al., 2013).

For what concerns action selection, a previous study, based on the presentation of non-lateralized stimuli but on the emission of lateralized responses, have found similar results. Daar and Pratt (2008), using a free-response task, reported that participants produced more left key-presses in responding to small numbers and more right key-presses in responding to large numbers. The relation between numbers and space has also been studied using other kinds of innovative paradigms. The magnitude of numbers randomly generated by adults humans was influenced by the side (left or right) they were facing. When participants turned their head toward the left they produced smaller numbers than when their head was turned toward the right (Loetscher et al., 2008). The influence of numerical magnitude on action has been demonstrated also during walking. Participants were required to generate random numbers while walking and to make a lateral turn. When the last numbers generated were relatively small participants turned left, while when the generated numbers were relatively large they turned right. Interestingly enough, lateral turn decisions could be predicted by the last few numbers generated prior to turning, suggesting an influence between numerical cognition and action (Shaki and Fischer, 2014). Also eyes movements are affected by numerical magnitude. Adults presented with a small digit (1 or 2) shifted their attention toward the left, while when presented with a large digit (8 or 9) they shifted their attention toward the right. This indicates that merely looking at numbers produces a corresponding shift of attention in the visual field (Fischer et al., 2003). More recently, by using a Posner-like task and non-symbolic numerousness (e.g., an array of dots), the effect of numerical magnitude on eye movements has been documented also in 8–9 month-old infants. Infants oriented their visual attention toward the left peripheral region of space in response to small numbers, while they oriented attention toward the right in response to large numbers (Bulf et al., 2015). These results suggest that the association between numbers and space occurs before the writing and reading acquisition undermining the idea that SNA is exclusively determined by culture. Data in support of this are obtained using a manual bisection paradigm. de Hevia and Spelke (2009) tested spatial-numerical association in adults, school children and pre-school children. All participants were required to indicate the midpoint of lines flanked by arrays composed of a different number of dots; the dots themselves essentially were an 'irrelevant' information. Participants of all ages presented the same bias: they bisected the line toward the right when the larger number of dots was shown in that direction (for similar results, see also Stöttinger et al., 2012). This phenomenon has been interpreted as a sort of 'cognitive' illusion by which the side ipsilateral to the larger (or smaller) numerosity is represented as longer (or shorter) and therefore the bisection bias toward the larger number compensates for this illusion. Data on the non-cultural origin of the spatial-numerical association are also supported by evidence on non-human animals. Day-old domestic chicks were trained to circumnavigate a panel located in the center of the apparatus and depicting a certain number of elements. At test they were presented with two panels, one located on the left and one on the right. When the panels depicted a number of elements smaller than the one experienced during training, birds circumnavigated the left panel. When the panels depicted a larger number, chicks circumnavigated the right panel (Rugani et al., 2015). Overall these findings showed that numerical magnitude influenced what was the selected response, suggesting that the coded magnitude information may reflect a link between numerical processing and actions (Rugani and Sartori, 2016). An effect of numerical magnitude on action selection in month-old and even day-old infants and in almost naïve animals suggest that SNA could be independent from everyday experience (for a review and discussion on this topic see McCrink and Opfer, 2014; Rugani and de Hevia, 2016). Our current results support this idea. Crucially, in our experiment we adopted a response task unbiased by intrinsic references to spatial-numerical representations (as you have using keyboards, for example) and we noticed that numerical magnitude influences action selection and execution.

This indicates that the responses of our participants were spatially biased by the numerical magnitude of the digit, also when performing a very unusual action. For what concerns the connection between numerical cognition and action planning, results of the few studies conducted up to now found comparable results. When participants were required to respond to numbers by grasping a small or a large object, they initiated faster a precision grip when responding to small numbers and a power grip when responding to large numbers (Lindemann et al., 2007). Similarly, participants required to grasp a wooden block and to move it according to the parity status of the numeral depicted on the block showed a larger grip aperture in grasping blocks depicting larger numbers than in grasping blocks of identical size but depicting small numbers (Andres et al., 2008b). In a subsequent study, participants were required to respond to the color of the ink with which digits were written on identical objects. Numerical magnitude, even if was task-irrelevant, affected grip aperture (Namdar et al., 2014). It has also been demonstrated that numerical magnitude processing influences the free choice of an object position (Gianelli et al., 2012). Participants were required to grasp a cube and to change its position, while performing a numerical discrimination task (i.e., indicating whether a presented digit was smaller or larger than 5). When responding to small numbers compared to larger ones, participants positioned the cube more leftward and closer to themselves. Moreover, in the initial phase of the grasp movement the grip aperture was modulated by the numerical magnitude (Gianelli et al., 2012).

While the association of left and right respectively to small and large numbers in previous literature could be explained by highly overlearned motor associations between numerical magnitudes and manual responses (Schwarz and Keus, 2004), our new and unusual task suffers less this objection. Moreover, our task enables the study of the association between actions and numerical magnitudes by means of kinematic analysis of movement. In future studies it will be interesting to selectively investigate the effect of numerical magnitude on the kinematic parameters of a same identical movement (e.g., kicking the ball always toward a central goal). This would avoid the left bias that we overall noted in the present task, due to the degrees of freedom of the right finger in relation with the anatomy of the right hand. The index is in fact asymmetrically more limited in its range of action by the middle finger on its right than by the thumb on its left.

Recent accounts have underlined the importance of finger-counting in number processing, as it leaves its mark in adulthood (Di Luca et al., 2006; Fischer, 2008), and it helps developing associations between numbers and hand actions. The origin of the relationship between numerical skills and finger counting is supported by different research. Abacus experts, while solving arithmetic calculation, show spontaneous hand movements (Hatano et al., 1977). Hubbard et al. (2005) suggested that the relation between finger counting and numerical cognition (the manumerical cognition hypothesis) could also explain why finger agnosia, left–right confusion and dyscalculia often co-occur in the Gerstmann syndrome.

The deep relation between numerical cognition and action has been explicated on the embodied cognition theory. This assumes that activation of bodily representations can help the comprehension of abstract concepts (Glenberg, 1997). As for other fields of cognition (Fischer and Zwaan, 2008) the embodied cognition theory has been proposed also for numerical concepts (Andres et al., 2008a; Lindemann et al., 2009). A challenge that this perspective offers concerns the use of embodied numerical cognition and associated movement tasks in teaching numerical concepts (Goldin-Meadow et al., 2009; Moeller et al., 2012). Moving hands help children in solving numerical problems (Moeller et al., 2012). Interestingly, enough, the positive effect of movement on numerical problem solving it is not limited to finger and/or hands but it is extended to the whole body. Different groups of first-graders participated to different trainings. A full-bodily experience training required to show the position of numbers by walking on a number line depicted on the floor. A non-full-bodily-experience training required to indicate the location of number on a tablet screen, using a computer-mouse. The full-bodily-experience training affected more positively the performance on math tasks than those who participated to a number line training which did not required a full-bodily experience (Link et al., 2013).

However, this is the first experimental demonstration of the relation between number cognition and motor action in a new and not-overlearned context. The employment of this paradigm will permit to untangle, from a very innovative perspective, the influence of biological and cultural factors in shaping the direction of the MNL and the role of finger in the acquisition of numerical skills. Moreover, our paradigm could be easily used to test whether the association between motor responses and space can be obtained also with auditory stimuli (for a recent demonstration of a spatial numerical association with auditory numerical stimuli, see Klichowskia and Króliczak, 2017). Last but not least, similar paradigms will allow to determine how cognition can influence action execution. A very recent paper by Pinheiro-Chagas et al. (2017) has in fact investigated the relation between simple arithmetic calculation (single-digit additions and subtractions) and finger movements. Participants were asked to point to the result of an arithmetic computation on a number line, while finger trajectory was constantly monitored. The analysis of trajectories unveiled that, during calculation, the two operands were serially processed. The finger first pointed toward the larger operand, then slowly deviated toward the correct result. This slow deviation was showed in subtractions and additions and it was proportional to the magnitude of the smaller operand (Pinheiro-Chagas et al., 2017). This evidence supports a previous finding on simpler numerical tasks (Song and Nakayama, 2009), highlighting that even complex mental operations can be continuously reflected in finger-pointing movements (Pinheiro-Chagas et al., 2017).

The employment of our innovative paradigm will not solely allow to understand the role of culture in shaping the direction of MNL, but it will also represent a simple and powerful method to disentangle the role of fingers in the acquisition of numerical skills.

ETHICS STATEMENT

The experimental procedures were approved by the Institutional Review Board at the University of Padua and were in accordance with the Declaration of Helsinki (Sixth revision, 2008).

AUTHOR CONTRIBUTIONS

RR and LS designed the study, created the stimuli, collected, analyzed the data, RR, FC, and LS did the statistical analyses; RR, SB, and LS interpreted the data discussed the results; SB, RR, and LS created the figures; RR and LS wrote the manuscript; SB and FC critically revised the manuscript.

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A Nap But Not Rest or Activity Consolidates Language Learning

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Recent evidence suggests that a period of sleep after a motor learning task is a relevant factor for memory consolidation. However, it is yet open whether this also holds true for language-related learning. Therefore, the present study compared the short- and long-term effects of a daytime nap, rest, or an activity task after vocabulary learning on learning outcome. Thirty healthy subjects were divided into three treatment groups. Each group received a pseudo-word learning task in which pictures of monsters were associated with unique pseudo-word names. At the end of the learning block a first test was administered. Then, one group went for a 90-min nap, one for a waking rest period, and one for a resting session with interfering activity at the end during which a new set of monster names was to be learned. After this block, all groups performed a first re-test of the names that they initially learned. On the morning of the following day, a second re-test was administered to all groups. The nap group showed significant improvement from test to re-test and a stable performance onto the second re-test. In contrast, the rest and the interference groups showed decline in performance from test to re-test, with persistently low performance at re-test 2. The 3 (GROUP) × 3 (TIME) ANOVA revealed a significant interaction, indicating that the type of activity (nap/rest/interfering action) after initial learning actually had an influence on the memory outcome. These data are discussed with respect to translation to clinical settings with suggestions for improvement of intervention outcome after speech-language therapy if it is followed by a nap rather than interfering activity.

Keywords: sleep, rest, words, interference, aphasia, memory, consolidation

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INTRODUCTION

> *"To sleep, perchance to dream; aye, there's the rub."*
>
> (William Shakespeare: Hamlet, Act III, Scene I).

Human adults spend about one third of their lifetime asleep (Alger et al., 2015). This state of reduced consciousness is a useful mechanism not only for physiological recreation but also for the consolidation of memory traces (Rechtschaffen and Kales, 1968; Diekelmann and Born, 2010; Diekelmann, 2014). During nocturnal periods of sleep[1], novel words and concepts get integrated into the existing semantic networks (Wang et al., 2016). In fact, there is a direct relationship between the duration of sleep and the amount of learning (Earle et al., 2017). On the other hand, patients with sleep disorders often suffer from impaired memory (Cellini, 2016). Moreover, there seems to be a distinction between procedural (implicit; not verbalisable; unintentional; often tested with motor sequences) and declarative (explicit, verbally expressible; intentional; factual) types of learning and memory (e.g., Squire and Zola, 1996).[2] Procedural learning (e.g., finger tapping sequences) relies more on phases of rapid eye movement (REM) sleep while declarative contents such as word association learning depends more on phases with sleep spindles (Philal and Born, 1997; for a recent review of the electrophysiological account of sleep-induced memory consolidation, which will not be part of the present paper, cf., e.g., Chatburn et al., 2014; or Rasch and Born, 2013). While both younger and aged subjects show such sleep-dependent memory consolidation for declarative contents, it is only the younger subjects for whom also procedural learning is supported (Pace-Schott and Spencer, 2015). The performance of healthy elderly participants in a procedural learning task after sleep is comparable to that after a waking period – only elderly stroke patients actually revealed positive effects of sleep after procedural motor learning (Backhaus et al., 2015; see also Gudberg and Johansen-Berg, 2015).

Importantly, it is not only nocturnal sleep that has a positive influence on memory consolidation. Short diurnal periods of sleep, i.e., naps, seem to exert positive influence on procedural/motor learning (e.g., Nishida and Walker, 2007; Seeck-Hirschner et al., 2010) and declarative/associative learning (e.g., Lahl et al., 2008). These supportive effects are particularly pronounced when the learning phase is followed immediately by the nap (Benson and Feinberg, 1977; Gais et al., 2006; de Bruin et al., 2016). When directly compared to a matched no-nap control group, a group enjoying a 70-min nap outperformed their controls at re-test in a procedural learning (juggling) experiment (Morita et al., 2016) and in a declarative (picture memory) study (Cellini, 2016).

However, other recent studies shed some doubt on the supportive role of a nap for motor learning. Although the meta-analysis by Pan and Rickard (2015) could confirm the overall effect of a bigger gain in groups with vs. without nap, the authors could explain that gain by the influence of moderator variables such as time of testing or training duration, rather than the sleep *per se*. In two studies using sequence learning and motor adaptation in a cross-over design, subjects were randomly assigned to wake, short nap, or long nap groups. The authors did not find any effect of sleep condition in either task.

Thus, it appears that for procedural motor learning, the debate cannot be concluded at this point. However, for declarative learning, in particular for language learning, the debate about the beneficial role of naps, i.e., shorter day-time sleeps with a maximum of one REM cycle, seems not to have even started yet. While it is widely agreed that (night) sleep positively impacts on vocabulary acquisition in infants (e.g., Axelsson et al., 2016), recent research in adults preferentially addresses the question of reduced amount and quality of overall sleep in older subjects on language learning (Kurdziel et al., 2016), or how learning during sleeping can be improved, e.g., by exposure of the sleepers to relevant foreign language cues (Schreiner and Rasch, 2016).

It is thus an open issue whether the relative benefit of a nap over waking, which is presently being disputed in the domain of procedural motor learning, can be found for vocabulary learning as a particular instance of declarative learning. Therefore, the present study addressed this question directly, comparing three groups of elderly healthy adults that completed a pseudo-word learning task followed by (a) nap, (b) passive rest, or (c) an interfering activity. By including elderly instead of younger adults, the study taps in particular into the distinction of procedural vs. declarative learning, since, as discussed above, older subjects' procedural learning is potentially unaffected by sleep or nap, whereas an influence on declarative language learning can be hypothesized (cf. Backhaus et al., 2015; Gudberg and Johansen-Berg, 2015; Cellini, 2016). If sleep in fact has a positive impact on the consolidation of language learning, this mechanism would be of potential use for the rehabilitation of aphasia after stroke, a condition that affects older people much more than young.

MATERIALS AND METHODS

All procedures were approved by the Institutional Review Board of the Medical Faculty of RWTH Aachen University.

Participants

For the study, healthy elderly subjects between 50 and 75 years of age were recruited. They grew up monolingually, with German as their native language and at least a high school degree (9 years of school; German "Hauptschulabschluss"). All subjects had normal or corrected-to-normal audition and vision. Exclusion criteria were a known history of psychiatric and/or neurodegenerative disease or other cognitive disability, regular intake of medication with potential effect on quality or quantity of sleep, and abuse of drugs or alcohol. Further exclusion criteria were acute sleep disorders, work in shifts, or participation in a foreign language class up to 6 months prior to the experiment.

A total of 30 volunteers were included in the study, forming three groups of $n = 10$ subjects each. The first group was going to have a nap, the second a phase of active rest, and the third an interfering activity task.

All groups were comparable with respect to years of education, age, level of day sleepiness, and daily amount of caffeine intake

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[1] Nocturnal sleep can usually be distinguished into different phases or cycles of 90–120 min, which can be further subdivided into Phases 1–4 representing increasing sleep depth, and a subsequent REM phase. The EEG reveals waves with frequencies <1Hz during slow-wave sleep, but theta rhythm (about 6–10 Hz) during REM phases. There are about 3–6 such cycles per night. There is still a lively debate about the neurophysiological mechanisms of learning and sleep ("sleep-assisted" vs. "Active System Consolidation" approaches) and their endocrinological basis (for a review cf. Gais and Born, 2004).

[2] Note that there has been a debate for over 50 years about the definitions and distinctions of "procedural vs. declarative" vs. "implicit vs. explicit" learning and memory (e.g., Frensch and Runger, 2003; Kihlstrom et al., 2007), which is still on-going.

(**Table 1**). The number of women was equally distributed among the groups [Freeman-Halton extension of the Fisher exact probability test for a 2-rows by 3-columns (instead of the typical 2 × 2) contingency table].[3]

Experimental Task

The core of the study was a pseudo-word learning task, after which the sample was split into three different interventions: daytime nap, active rest, or interference (see below). This pseudo-word learning task was designed as follows. A set of 24 images of fantasy "monsters" was obtained from www.shutterstock.com. Each monster was given a name that was a 1- to 3-syllabic pseudo-word in German, obtained by the exchange of one or more vowels from real German words (words taken from the dissertation by Mouson, 2009). An equal number of 1-, 2-, and 3-syllabic names was given to the 24 monsters.

This set was then divided into two sub-sets (A and B). The items of set A were used for the pseudo-word learning task prior to the intervention phase for all subjects. The experiment consisted of three runs, which were prepared by the in-house *Audio-Visual Media Center* as time-locked video (mpg) presentations for a laptop computer screen. During each run, all monsters were presented in a quiet, normally lit room in randomized order for 10 s each, with a 2-s inter-stimulus interval with a blank black screen. While the image of a monster was on the screen, its name was presented twice via loudspeakers connected to the laptop, once after 1 s and then again at second 5. A schematic of the learning phase of the study can be found in **Figure 1**. Subjects were instructed to memorize the name of the monster at that time.

Study Design

Prior to participation, the subjects were informed about the study design and purpose, and the absence of any exclusion criteria was confirmed. All subjects signed the informed consent sheet. The experimental procedures were approved by the Institutional Revision Board of the Medical Faculty at RWTH Aachen University.

On Day 1, subjects were not allowed any caffeine or nicotine 2 h prior to the experiment. At 9:00 a.m., they were received by the experimenter and completed the sleepiness questionnaire. Then, at 9:30 a.m., the learning task was performed. At 9:45 a.m. their learning achievement was tested. The tests consisted of the presentation of each of images of the monsters in a pseudo-randomized order which differed at every test. Subjects were asked to recollect as many names as they could. They were not put under time pressure for their overt uncued naming response. The response was written down by the experimenter in a standardized protocol sheet and analyzed later for correctness by trained speech-language therapists. The data were cross-validated by at least one other rater.

Next, the subjects of the Nap group were offered the opportunity of a 90-min[4] nap in a quiet room. The experimenter ensured that the subjects fell asleep and, if necessary, woke them up after 90 min. A polysomnographic examination was not conducted. The subjects of the Rest group were taken to a quiet room where they remained awake for 90 min painting mandalas, building Jenga® towers or playing the Solitaire card game, i.e., non-verbal activities. They were not allowed any caffeine or nicotine during that time; only herbal infusions or mineral water were allowed. The Interference group received the same treatment as the Rest group with one modification: At the end of the rest period there was another pseudo-word learning task with a different set of stimuli for 10 min providing retroactive interference to the previous learning experience (cf. Korman et al., 2007). Then, all subjects performed the pseudo-word test a second time (*Re-Test 1*; 90-min re-test).

After that, all subjects went home. They came back on Day 2 at the same time as on Day 1 in order to perform the pseudo-word test again (*Re-Test 2*, 24-h re-test) in order to account for the effect of nocturnal sleep on the consolidation process. The study design is depicted in **Figure 2**.

Statistical Analysis

Statistical analysis was performed with SPSS 20.0 (SPSS Corp., 2011). First, the initial level of performance of the three groups was compared to ensure equality of groups in this respect. Next, a 3 × 3 ANOVA with factors INTERVENTION (Nap/Rest/Interference) and TIME (Test/Re-Test1/Re-Test2)

TABLE 1 | Characterization of the three experimental groups (mean ± SEM).

Variable [unit]	Nap	Rest	Interference	*p*
Age (years)	62.6 (1.8)	59.9 (1.6)	60.0 (1.5)	0.432
Education (years0	11.9 (0.6)	10.4 (0.6)	11.7 (0.5)	0.148
Day sleepiness* (ESS score)	4.4 (0.8)	6.5 (0.9)	4.7 (0.8)	0.181
Daily caffeine intake (cups)	4.2 (0.8)	4.4 (0.7)	2.6 (0.4)	0.136
n (female)	6	7	5	0.526
n (total)	10	10	10	

*The last column refers to the test of comparability between groups: one-way ANOVA for Age, Education, Sleepiness, and Caffeine; Freeman-Halton extension of the Fisher exact probability test for number of women per group. * Epworth Sleepiness Scale (Johns, 1991).*

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[3] http://www.vassarstats.net

[4] It appears that REM sleep deprivation affects learning more than slow-wave sleep deprivation (for a review see Curcio et al., 2006). Since one sleep cycle which ends with the REM sleep phase usually lasts 90 min, we decided to use this duration rather than that of 70 min (Cellini, 2016; Morita et al., 2016), during which time the relevant REM period might still be missing – even though the sleep cycles become shorter with increasing age (Schulz, 1997).

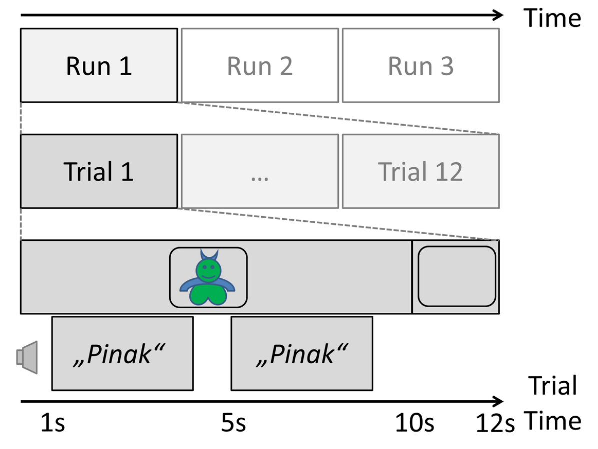

FIGURE 1 | Trial schema of the learning phase of the experiment before the nap/interference manipulation.

was conducted. Subsequently, planned pair-wise comparisons between Test, Re-Test1, and Re-Test2 were calculated individually for each group. The original (uncorrected) *p*-values as provided by SPSS are reported, but effects were only considered significant if they also survived Bonferroni correction. Finally, in order to understand the role of potential influence factors on the learning success, bivariate correlation coefficients were calculated in an exploratory manner.

RESULTS

The language learning scores for the three groups at each time point are displayed in **Figure 3**.

Comparison of Intervention Effects between Groups

The 3 × 3 ANOVA revealed significant main effects of INTERVENTION [$F(2,27) = 10.147$; $p = 0.001$] and TIME [$F(2,54) = 10.473$; $p < 0.001$] and a significant INTERVENTION × TIME interaction [$F(4,54) = 15.374$; $p < 0.001$].

Planned Contrasts for the Nap Condition

The *post hoc* two-tailed dependent-sample *t*-tests for the Nap group revealed a significant increase in language learning from Test to Re-Test1 [$t(9) = -3.280$; $p = 0.010$] and from Test to Re-Test2 [$t(9) = -3.207$; $p = 0.011$]. There was no difference between Re-Test1 and Re-Test2 [$t(9) = -0.557$; $p = 0.591$ two-tailed].

Planned Contrasts for the Rest Condition

The *post hoc* two-tailed dependent-sample *t*-tests for the Rest group revealed a significant decrease in language learning from Test to Re-Test1 [$t(9) = 3.973$; $p = 0.003$ two-tailed]. All other effects were not significant at a corrected level [Re-Test1 to Re-Test2: $t(9) = -2.449$; $p = 0.037$ two-tailed; Test to Re-Test2: $t(9) = 2.090$; $p = 0.066$ two-tailed].

Planned Contrasts for the Interference Condition

The *post hoc* two-tailed dependent-sample *t*-tests for the Interference group revealed a significant decrease in language learning from Test to Re-Test1 [$t(9) = 5.582$; $p < 0.001$] and from Test to Re-Test2 [$t(9) = 5.014$; $p = 0.001$]. There was no difference between Re-Test1 and Re-Test2 [$t(9) = 1.152$; $p = 0.279$ two-tailed].

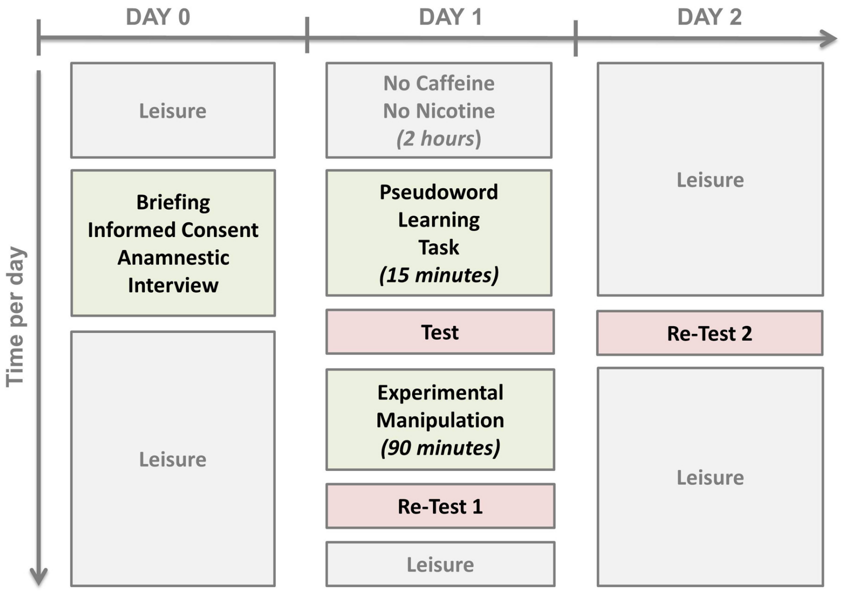

FIGURE 2 | Study Design.

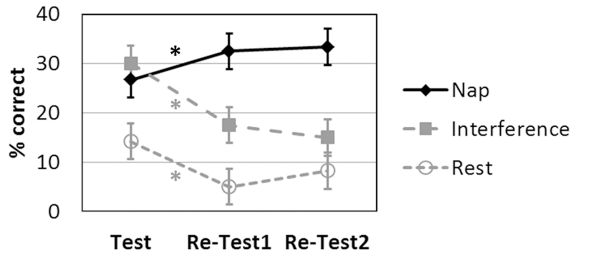

FIGURE 3 | Language learning achievement (recall) over time (Test: after the initial learning session; Re-Test1: immediately after nap/rest/interference; Re-Test2 on the next day) as a function of intervention. *$p < 0.05$ Bonferroni-corrected. Symbols represent average percent correct performance per group, error bars indicate the standard errors of mean.

Comparability of Groups before Intervention

In order to test whether the numerical differences in the initial level of performance after the pseudo-word learning session at the first Test had any influence on the results, a one-way ANOVA with factor INTERVENTION was conducted. This ANOVA showed a significant main effect [$F(2,27) = 5.407$; $p = 0.011$]. Subsequent *post hoc* comparisons (least square difference method, uncorrected for multiple comparisons providing maximum sensitivity for the existence of a difference under the assumption that no difference exists) revealed that the Rest group had lower performance than both other groups (Interference vs. Nap: $p = 0.517$; Interference vs. Rest: $p = 0.004$; Nap vs. Rest: $p = 0.020$).

Comparison of Intervention Effects between Groups with Initial Performance as Covariate

Consequently, the original 3 × 3 ANOVA was re-run as an ANCOVA with the subjects' individual performances at the first test as covariate. In this ANCOVA, the main effect of INTERVENTION was significant [$F(2,26) = 23.000$; $p < 0.001$]. Likewise, the INTERVENTION × TIME interaction remained significant [$F(4,52) = 16.029$; $p < 0.001$]. Only the main effect of TIME disappeared [$F(2,52) = 0.241$; $p = 0.787$].

Correlation Analysis

The potential influence factors for learning outcome at Test (index T0), Re-Test1 (index T1), and Re-Test2 (index T2) were submitted into a series of correlation analyses with the initial test performance to identify any circumstances that might have differentially affected the later performance in the experiment. These factors were "years of education," "biological age," "day sleepiness," and "caffeine intake." The analysis revealed no systematic effects whatsoever: years of education ($p_{T0} = 0.677$; $p_{T1} = 0.441$; $p_{T2} = 0.592$), age ($p_{T0} = 0.750$; $p_{T1} = 0.606$; $p_{T2} = 0.732$), day sleepiness ($p_{T0} = 0.228$; $p_{T1} = 0.272$; $p_{T2} = 0.631$), caffeine intake ($p_{T0} = 0.944$; $p_{T1} = 0.305$; $p_{T2} = 0.249$).

DISCUSSION

The present study sought to investigate whether a day-time nap may have a beneficial effect on language (vocabulary) learning in elderly subjects as compared to 90 min of active rest with or without interfering activity. The motivation was twofold: For one, the theoretical issue emerged from the literature review which revealed a vivid debate in the realm of procedural/motor learning but no comparable wealth of data for declarative/language learning. Moreover, the issue is of clinical relevance for the design of rehabilitation of patients with aphasia after stroke: Should periods of sleep be introduced as parts of the therapy, rather than providing interference to the speech-language therapy by some other therapeutic activity (cf. Siengsukon and Boyd, 2008, for the relevance to include sleep phases in the therapeutic schedule)?

The findings are straight-forward. There is a clear interaction of intervention and time on the pseudo-word learning task performance. Subjects in the Nap group profited significantly in their performance, whereas the subjects in the Rest and the Interference groups showed a significant decline in performance instead that was not compensated by the subsequent night sleep. The data thus replicate and extend earlier work on the role of sleep and nap for declarative learning (word recall) by Lahl et al. (2008), demonstrating that the association of pictures with novel pseudo-word names can also benefit from a day-time nap. The present study thus opens a novel perspective for the clinical application where confrontation naming in aphasic patients with word finding difficulties is still a standard procedure. Taking into account the suggestion by Gudberg and Johansen-Berg (2015) for inclusion of sleep into the therapeutic schedule and the meta-analytic findings by Backhaus et al. (2015) that stroke patients may show sleep-supported learning, the data from the present study may initiate further research in the realm of speech-language therapy.

Another facet that this study adds to the existing literature is the juxtaposition of passive rest and active interference. Even though the data for these two non-nap groups show comparable temporal trajectories, it might be worth investigating further whether, and if so, at what point, interference might disturb consolidation more than mere rest (cf. Shadmehr and Brashers-Krug, 1997; Korman et al., 2007; for the protective effect of sleep *after* interference see Ellenbogen et al., 2007; or Ertelt et al., 2012). In the present study, the time interval between the learning task and Re-Test 1 was 10 min longer for the Interference group than for the Rest group due to the additional interference task and since the actual rest period was supposed to be comparable between groups, ensuring comparability also with the 90 min nap in the Nap group. Subsequent studies investigating the manipulation of the retention intervals between Test and Re-Test1 might provide additional insights into the stability of the effects.

Moreover, the present study also contributes to the distinction between procedural/motor and declarative/language learning, showing that several study designs from the former domain might be re-run in the latter. This holds in particular for the question whether older subjects can, or cannot, profit from the potentially consolidating effect of sleep on learning performance. The meta-analysis by Backhaus et al. (2015) and their subsequent empirical studies (Backhaus et al., 2016a,b) suggested that sleep has no such effect on older subjects in motor learning paradigms. The data presented here could be taken to indicate that the consolidation mechanisms behind declarative/language learning may be different to some extent (see, e.g., Philal and Born, 1997, or Gais and Born, 2004, for a discussion of the distinctive relevance of REM vs. slow-wave sleep for the consolidation in procedural vs. declarative learning tasks). Electrophysiological or neuroimaging models were not part of this study (cf. Chatburn et al., 2014; Peigneux, 2015; or Rothschild et al., 2016); however, the present study might serve as an inspiration to compare the neurophysiological pathways by which sleep differentially modulates procedural and declarative learning, and to what extent that knowledge may be translated to clinical application.

Despite the clear pattern of results, several potential limitations should be considered. For one, the sample size with $n = 30$ is not large. Even though all effects of the experimental manipulation and their interaction were significant, a higher power might help better distinguish consolidating effects also from the nocturnal sleep periods.[5] This is of particular importance since other studies of procedural (Morita et al., 2016) and declarative (Cellini, 2016) learning also observed performance improvement in non-sleep control groups. One potential explanation for the absence of such positive learning effect in the present study could be derived from King et al. (2015; see discussion in King et al., 2017), who argue that a low performance level at the first test provides only little chance of consolidation.[6] This was exactly the situation for the Rest group, whose initial performance was below that of the other two sub-groups. Even though we considered the initial performance level as a covariate, and despite the lack of any significant correlations of the demographic variables with test performance, it could be that higher performers would have better consolidation. Finally, subsequent studies might make use of cross-over designs for Nap/Rest/Interference to control for between-group differences not only statistically (as done here) but also by virtue of the study design itself.

CONCLUSION

We were able to demonstrate that a day-time nap has a positive, consolidating effect on language (i.e., vocabulary or pseudo-word name) learning which exceeds effects of the same intensity of active rest or interfering activity, possibly due to the slow-wave sleep and/or REM sleep phases that are absent during mere rest. The clinical potential of this approach for speech-language therapy remains to be investigated both for the direct application but also for the theoretical background, e.g., in order to test how complex words or even syntactic utterances profit from naps, or how the degree of impairment of the patients (i.e., their pre-treatment level of performance interacts with the protective effects of sleep). For all these future directions, the present study provides a first stepping stone. Finally, it should be noted the present findings do not rule out (and were not indented to do so) the influence of other relevant factors on learning in the procedural or declarative domain or even their interaction, and their potential implications for the treatment of patients (cf., e.g., Schack et al., 2014, for a recent example of how motor imagery not only increases the efficacy of motor learning in healthy adults but may serve as a substitute for actual physical practice in injured participants).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen.

AUTHOR CONTRIBUTIONS

SH: Concept, study design, translation to clinical setting, data analysis, discussion, and writing of manuscript. JK: Concept, study design, data analysis, discussion, and revision of manuscript. KS: Concept, study design, concept for translation to clinical setting, data analysis, discussion, and revision of manuscript. SB: Study design, data acquisition, data analysis, discussion, and revision of manuscript. GB: Study design, data acquisition, data analysis, discussion, and revision of manuscript. NN: Study design, data acquisition, data analysis, discussion, and revision of manuscript. LS: Study design, concept for translation to clinical setting, discussion, and revision of manuscript. FB: Concept, study design, data analysis, discussion, and revision of manuscript. CW: Concept, study design, concept for translation to clinical setting, data analysis, discussion, and revision of manuscript.

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The analyses in this paper are based on raw data acquired by NN, GB, and SB during the course of their M.Sc. projects. Their original study documents are archived by them accordingly.

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[5] This is of particular importance for the subjects in the Rest group for whom a performance increase after night sleep was present and only failed to reach significance at a corrected level.

[6] As to the overall comparably low performance at Test1, one has to keep in mind that arbitrary colored monsters were assigned meaningless, i.e., pseudo-word, names. The subjects did not learn "real" vocabulary of a novel language which could be integrated into an existing semantic network.

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Functional and Structural Neuroplasticity Induced by Short-Term Tactile Training Based on Braille Reading

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Neuroplastic changes induced by sensory learning have been recognized within the cortices of specific modalities as well as within higher ordered multimodal areas. The interplay between these areas is not fully understood, particularly in the case of somatosensory learning. Here we examined functional and structural changes induced by short-term tactile training based of Braille reading, a task that requires both significant tactile expertise and mapping of tactile input onto multimodal representations. Subjects with normal vision were trained for 3 weeks to read Braille exclusively by touch and scanned before and after training, while performing a same-different discrimination task on Braille characters and meaningless characters. Functional and diffusion-weighted magnetic resonance imaging sequences were used to assess resulting changes. The strongest training-induced effect was found in the primary somatosensory cortex (SI), where we observed bilateral augmentation in activity accompanied by an increase in fractional anisotropy (FA) within the contralateral SI. Increases of white matter fractional anisotropy were also observed in the secondary somatosensory area (SII) and the thalamus. Outside of somatosensory system, changes in both structure and function were found in i.e., the fusiform gyrus, the medial frontal gyri and the inferior parietal lobule. Our results provide evidence for functional remodeling of the somatosensory pathway and higher ordered multimodal brain areas occurring as a result of short-lasting tactile learning, and add to them a novel picture of extensive white matter plasticity.

Keywords: neuroplasticity, primary somatosensory cortex, secondary somatosensory cortex, sighted, Braille, fractional anisotropy

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INTRODUCTION

Neuroplastic changes accompanying the processes of new skill acquisition or associative learning have been studied in both humans and animals. It is well established that following sensory learning, the cortex of the modality specific to the task shows modifications in electrophysiological properties, neuronal responsiveness, synaptic, and functional connectivity, gray matter volume, and the structure of white matter (for review see: de Villers-Sidani and Merzenich, 2011; Kilgard, 2012; Zatorre et al., 2012; Lövdén et al., 2013; Sur et al., 2013; Takeuchi and Izumi, 2013).

In the somatosensory domain, tactile sensory discrimination was reported to alter receptive fields and excitability of neurons of the primary somatosensory cortex, and induce representational plasticity in both humans and animals (Recanzone et al., 1992; Siucinska and Kossut, 1996 Pleger et al., 2003; Gebel et al., 2013; Ladda et al., 2014; Andrew et al., 2015). Rapid recruitment of the primary visual cortex for touch after short-term visual deprivation (Merabet et al., 2008) and alterations in activity of supramodal cortical regions have also been shown (Pleger et al., 2003; Saito et al., 2006; Eckhoff et al., 2008; Groussard et al., 2010; Sathian et al., 2013).

Sensory learning was also found to increase neuronal excitability in animal learning models (Saar and Barkai, 2003; Ohl and Scheich, 2005; Matthews and Disterhoft, 2009; Bekisz et al., 2010) and stronger activation may induce increases in myelination (Sampaio-Baptista et al., 2013; Gibson et al., 2014; McKenzie et al., 2014) or axonal sprouting (Beaulieu, 2002; Boele et al., 2013), which may be reflected by its fractional anisotropy (FA). Moreover, only a few functional activation studies were combined with investigation of white matter integrity (Scholz et al., 2009; Taubert et al., 2010; Loui et al., 2011; Gebauer et al., 2012; Schlegel et al., 2012; Lövdén et al., 2013; Draganski et al., 2014; Chavan et al., 2015) and none of them focused on tactile learning.

To address this issue, we investigated the patterns of functional and structural reorganization induced by tactile learning. The learning task was to read Braille exclusively by touch. Our subjects were individuals with normal vision who had no prior experience with the tactile Braille alphabet. Braille reading consists of several distinct processes including simple finger movement, the perception of series of variously arranged raised dots, pattern recognition, and semantic decoding/lexical processing. Learning to read Braille combines mastering the tactile discrimination task with higher cognitive functions. Since the somatosensory modality plays a crucial role in this process, we expected to find changes along the somatosensory pathway including the primary (SI) and secondary somatosensory (SII) cortices, as well as other areas of the ventral somatosensory pathway engaged in processing of tactile information (Burton and Sinclair, 2000; Pleger et al., 2003; Reed et al., 2004).

While use-dependent plasticity within the primary somatosensory representation is well documented, much less attention has been paid to the secondary somatosensory area. The SII is a higher-order, somatotopically organized cortical area known for its participation in tactile and learning processes, decision making, and susceptibility to the influence of attention (Johansen-Berg et al., 2000; Fujiwara et al., 2002; Romo et al., 2002; Sadato et al., 2002; Pleger et al., 2003). It is also considered to be a multimodal area that integrates information from both sides of the body (Huttunen et al., 1996), but its exact role is still unknown. We previously reported bilateral plasticity of the vibrissae representation within the SII of mice resulting from a short-term sensory training, which was the first demonstration of functional changes to this area induced by associative learning in rodents (Debowska et al., 2011). Unilateral structural (voxel based morphometry, VBM) change of the SII cortex associated with tool-use learning was reported in primates by Quallo et al. (2009). Therefore, the second objective of our study was to understand the relative contributions of the somatosensory cortices to learning by determining whether the secondary somatosensory cortex in humans also undergoes neuroplastic changes induced by sensory training.

Besides somatosensory areas, we expected to observe training-induced changes within multisensory cortical regions known to be involved in tactile recognition: the fusiform gyrus/lateral occipital cortex and associative parietal areas (Amedi et al., 2001, 2002; Sadato et al., 2002; Kassuba et al., 2011; Kim and Zatorre, 2011; Marangon et al., 2016).

METHODS

In the present study, a group of sighted individuals underwent two scanning sessions (fMRI and DTI) before and after they learned to read Braille exclusively by touch, without any visual deprivation (subjects also kept their eyes open during trainings and MRI sessions).

Participants

21 right-handed and sighted subjects (11 women, 10 men, min. age = 22, max. age = 26, mean age = 24.1, *SD* = 1.4) with no history of neurological or psychiatric disorders participated in the study (Oldfield, 1971). All participants gave their written informed consent prior to the start of the experiment and received financial compensation for completed participation. None of the subjects had prior experience with Braille reading. The study was approved by the Ethics Committee of the Warsaw Medical University.

Experimental Procedure—Braille Training

Training consisted of 15 Braille reading lessons (45 min per day) conducted over the course of 3 weeks. The Braille teaching procedure was planned under the supervision of the Polish Association of the Blind. A Braille 36-chapter ABC-book printed on plastic with standard Braille dimensions (Marburg Medium) was used for the purpose of learning to read Braille (Andraszewski, 2006). As the ABC-book is designed for use by visually-impaired people, it enables us to explore and learn subsequent Braille characters exclusively by touch. The new skill of Braille character recognition was acquired by tactile association with embossed (same-size dots) letters of the Latin alphabet. The first couple of chapters introduced the Braille alphabet with the subsequent ones providing exercises and readings solely in Braille. The six-dot cell (rectangles) used in a further part of the experiment for non-Braille tactile recognition (control) did not appear during the training, so this particular spatial dot-pattern remained untrained and ascribed no particular meaning. The greatest emphasis of the training was put on practice, such that the first lesson included reading a series of up to six-letter words. Subjects were trained to use only their index finger of the right hand while learning, while the left hand was used to guide the right hand position on the text. Participants kept their eyes open during the trainings and the Braille text was concealed by a partition. Additionally, they were asked not to look up the visual Braille displays. Trainings were conducted in small groups (3–4 people) by the same teacher. Great care was taken to teach each subject in the same manner and to a similar skill level. The first nine chapters introduced letters, so during trainings subjects repeatedly returned to them throughout the entire course. After completing the basic lessons, subjects were trained in reading short words and then short sentences that comprised short stories. Since reading skill was balanced among the group, subjects were able to progress up to the 30th chapter over 15 sessions.

Brain Imaging

The first brain imaging session was conducted 1 day before beginning the trainings and the second session 1 day after the last training.

fMRI—Braille Character Discrimination Task

During the functional imaging sessions, the subjects were asked to actively explore and compare two simultaneously presented Braille characters or non-Braille signs (six-dot rectangles; **Figure 1A**), or simply to move their finger as though they were touching the presented stimuli, but without touching the matrix (control task). The stimuli were perceived by an active touch of the "trained" finger. A total of 32 pairs of Braille characters (chosen from all of the letters of the alphabet, half of which were the same) and 32 pairs of either parallel or shifted positioned rectangles were presented pseudorandomly alternating with 32 simple movement trials, with a constraint of no more than three consecutive trials of the same type in a row. The functional data were obtained using an MRI-compatible Braille Character Stimulator, fully computer-controlled, phneumatically driven, and capable of delivery up to three standard Braille characters simultaneously (2 × 3, Marburg Medium) with addition of delivery also diacritics and meaningless characters i.e., rectangles (for detailes see: Debowska et al., 2013). The stimulator was placed on the subject's thigh, so the arm laid naturally along the body and the "reading" finger was positioned as when reading regular text. Subjects were requested to look at a fixation cross ("+") located in the center of a black screen during the whole session. Change of the fixation point color was used as a cue. The sequence of colors in a single experimental trial was as follows: starting with white (basic color), a yellow "+" is presented for 2 s as a preparatory cue. The "+" then turns green and the stimuli are presented for 3.5 s, after which it turns back to white. After a few seconds it turns red to signal time for a response and then reverts back to white. In the "movement" condition trials, conducted in order to identify brain activations associated with finger movement *per se*, the preparatory cue was presented in blue. Intra- and inter-trial intervals varied across tasks and were administered randomly for 4 to 6 s and 4 to 10 s, respectively. Examples of tactile stimuli and a single trial sequence schema are presented in **Figures 1A,B** respectively. The delay between the stimulation and the response cues was introduced in order to obtain "pure" activation from unilateral stimulation. Subjects submitted their answers by pushing the corresponding button on a ResponsePad® (SMIT-LAB, www.smit-lab.eu) with their left hand. The software package PRESENTATION® (Neurobehavioural Systems, Albany, CA) was used to present stimuli and register subjects' responses. The stimuli application procedure used for the active tactile discrimination task in this study guaranteed precise (Braille) stimuli size, resolution, and presentation timing.

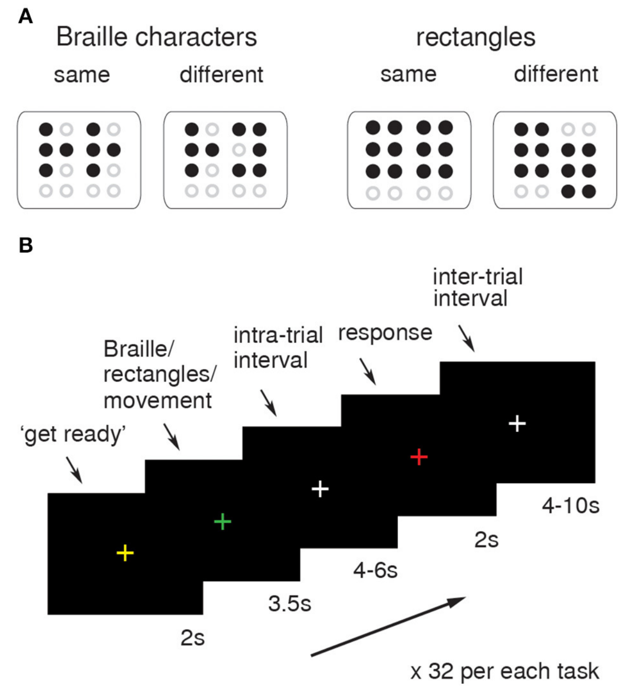

FIGURE 1 | fMRI procedure. Examples of same-different Braille characters and rectangles used as tactile stimuli during functional run **(A)**. The schema of the visual presentation used as a task-cue for subjects. The change of the fixation cross ("+") was coupled with tactile (Braille/rectangles) stimuli presentation and submission of answers **(B)**.

MRI Acquisition

All images were acquired on a 3T MRI scanner (Magnetom Trio TIM VB17, Siemens Healthcare, Germany) using a 12-channel head matrix coil. All subjects underwent two identical scanning sessions: before and after the Braille training. Detailed anatomical, functional, and diffusion-weighted images were acquired during both sessions.

fMRI Data Acquisition and Analysis

Anatomical data (T1-weighted) were obtained with 1 mm isotropic resolution (TR = 1900 ms/TE = 2.2 ms/FA = 9 deg./FOV = 192 mm/IPAT = 2/TA = 22:11 min, 47 axial slices perpendicular to AC-PC line). In the functional run a total of 440 volumes (plus 5 dummy scans) were obtained during Echo-Planar Imaging sequences with the following parameters: TR = 3000 ms/TE = 30 ms/voxel: 2 × 2 × 3 mm/FA = 90 deg. SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) was used for data preprocessing and analysis. First, functional images were motion corrected. Then, structural images from single subjects were co-registered to the mean functional image. In the next step, T1 images were warped to the MNI (Montreal Neurological Institute) T1 image template (voxel size of 2 × 2 × 2 mm), and normalization parameters were applied to the functional images, wherein these data were smoothed using a 5-mm isotropic Gaussian kernel. A high-pass filter with a 128 s cutoff was applied to remove low-frequency fluctuations in the BOLD response. For each subject and for each time period separately (before and after training), the onsets and stimuli durations were entered into the design matrix and modeled in a general linear model according to different event types. Regressors were convolved with the canonical hemodynamic response function (Friston et al., 1995). Specific condition effects were assessed by the application of linear contrasts, where parameter estimates for events (i.e., discrimination of Braille characters) were compared to the movement condition. Overall, there were four planned contrasts of interest at the first level of analyses: Braille vs. movement and Braille vs. rectangles each before and after the training. At the second level (whole-brain), paired *t*-tests were used: Braille > movement $_{\text{after > before}}$ and Braille > rectangles $_{\text{after > before}}$. The statistical threshold was set at $p < 0.001$ and corrected to $p < 0.05$ for multiple comparisons (Family Wise Error) at the cluster-level using cluster size. Detailed results of statistical analysis with MNI coordinates for peaks, clusters size, and exact values used as an extent thresholds are presented in **Table 1**. Statistical parametric maps for appropriate comparisons superimposed on the gray matter template (GM tissue probability map) are presented in **Figures 2**, **3**. Percentage of signal change was calculated individually within a spherical volume of interest with a diameter of 10 mm using Marsbar (Brett et al., 2002) and then compared using paired *t*-test.

DTI Protocol and Analysis

Spin-echo diffusion weighted echo planar imaging (DW-EPI) sequence was performed with an isotropic (2 × 2 × 2 mm) resolution, *b*-value of 1000 s/mm^2, 64 gradient directions and repeated twice in order to increase signal-to-noise ratio. The eddy distortion correction and diffusion tensor parameter estimation were performed using ExploreDTI (Leemans et al., 2009). Fractional anisotropies (FA) were calculated for each subject before and after training. SPM12 was used for motion correction, normalization procedures including co-registration to the FA template, smoothing using 3-mm isotropic Gaussian kernel algorithm, and statistical analysis employing paired *t*-tests (Abe et al., 2010). The statistical threshold was set at $p < 0.001$ and corrected to $p < 0.05$ for multiple comparisons (Family Wise Error, FWE) at the cluster-level using cluster size. Detailed results of statistical analysis with MNI coordinates for peaks, clusters size, percentage of FA change, and the exact values used as extent thresholds are presented in **Table 2**. Statistical parametric maps superimposed on the white matter template (WM tissue probability map) are presented in **Figure 5**. Anatomical localization of cortical and white matter regions was verified on the basis of the MNI Space Utility and confirmed manually using the Atlas of the Human Brain and the MRI Atlas of Human White Matter (Mai et al., 2007; Mori et al., 2010).

RESULTS

Behavioral Results

Braille Discrimination (Same-Different) Task

Task performance (percentage of correct responses) differed significantly from the first to the second imaging session. A paired *t*-test ($t = 31.46$, $df = 20$) revealed a significant improvement from 37.5% (min. = 34.3, max. = 37.5, $SD = 4.4$) to 91.85% (min. = 90.6, max. = 96.8, $SD = 6.3$) in the Braille character discrimination task performance ($p < 0.001$).

Rectangles Discrimination Task

Comparisons of non-Braille discrimination task performance before and after a posteriori did not reveal significant differences ($t = 2.13$, $df = 20$). In the first session the mean percent of correct responses was 56.9% (min. = 53.1, max. = 68.7, $SD = 7.6$), while in the second session it reached 61.4% (min. = 46.8, max. = 75, $SD = 8.2$).

fMRI Results

We analyzed brain activation patterns accompanying discrimination of Braille characters performed by active touch, before and after a short-term intensive tactile training of Braille reading in sighted subjects ($N = 21$). Statistical parametric maps of task-related brain activity patterns before and after the Braille-based tactile training separately are shown in Supplementary Materials. The Braille discrimination vs. finger movement comparison showed a similar pattern of activity across the brain with stronger activations after the training (**Figure S1A**); comparing Braille vs. rectangles revealed a massive reorganization of cortical activation within the left hemisphere (**Figure S1B**). Analysis of the interaction between the two imaging sessions (after vs. before) and the experimental conditions revealed a set of brain areas that changed their activation as result of the training (**Figures 2**, **3**). A detailed description is given below and the full set of obtained results along with statistics is given in **Table 1**.

The Effects of Braille-Based Tactile Training

Braille Characters Discrimination Task > Finger Movement $_{\text{after > before}}$

By contrasting the brain activity pattern involved in the Braille discrimination task and motion activity without touching (movement), we aimed to depict the cortical underpinnings of Braille-related somatosensory information processing. Comparing the Braille character discrimination task-related activity to the simple finger movement condition showed a wide network of cortical regions involved in this specific activity before and after the training. Our analysis indicated several structures within this network presenting more pronounced responses while performing the Braille character discrimination task after the training. Notably, a bilateral increase in activity of the primary somatosensory representation (SI) was observed. Stronger activations were also found in the precuneus and the angular gyrus located within the left hemisphere, and in the bilateral inferior parietal

TABLE 1 | Regions showing significant increases in activation as a result of the Braille training (Braille discrimination vs. control tasks × session interaction).

***k* = 95**	***x***	***y***	***z***		**Cluster**	***T* (peak)**
BRAILLE > MOVEMENT$_{\text{/AFTER > BEFORE}}$						
Postcentral Gyrus (SI)	−40	−52	60	L	576	7.17
	−42	−50	56			6.84
Inferior Parietal Lobule	−44	−36	46			7.51
	−36	−42	44			6.58
Angular Gyrus	−28	−74	40	L	332	6.16
	−28	−64	46			5.53
Precuneus	−22	−76	56			4.59
Postcentral Gyrus (SI)	40	−56	58	R	215	7.18
	44	−50	60			5.69
Posterior Cingulate Cortex	0	−34	32	L/R	208	5.83
	2	−32	22			5.37
Middle Frontal Gyrus	−44	46	4	L	176	5.73
	−46	38	14			5.30
	−50	34	20			4.75
Middle Frontal Gyrus	50	36	22	R	151	5.67
	44	34	28			5.40
Inferior Parietal Lobule	36	−48	42	R	122	5.48
	42	−42	40			4.66
Fusiform Gyrus	−50	−52	−16	L	102	6.91
Fusiform Gyrus	56	−54	−14	R	100	5.31
	56	−42	−10			5.02
Insula	38	20	2	R	95	5.72
	46	18	−6			4.42
***k* = 78**						
BRAILLE > RECTANGLES$_{\text{/AFTER > BEFORE}}$						
Postcentral Gyrus (SI)	−38	−56	58	L	1392	9.85
	−42	−50	60			7.32
Angular Gyrus	−32	−84	38			7.19
	−32	−72	42			6.89
Inferior Parietal Lobule	−32	−48	56			6.59
Precuneus	−18	−72	52			5.48
	−20	−68	54			5.3
Middle Frontal Gyrus	−40	10	30	L	399	6.79
Inferior Frontal Gyrus	−42	26	34			6.09
	−42	28	26			6.09
Posterior Cingulate	−2	−38	24	L/R	190	5.76
	−2	−30	36			5.65
	6	−24	24			4.50
Fusiform Gyrus	−50	−56	−18	L	100	7.19
	−40	−52	−16			3.94
Middle Frontal Gyrus	30	−2	64	R	93	6.11
Superior Frontal Gyrus	30	−2	64	R	93	6.11
	28	8	58			4.75
Precuneus	16	−70	62	R	78	5.86
	26	−68	60			5.45

T-values of the peak activations, $p < 0.05$ (correction for multiple comparisons at cluster level, Family Wise Error), and extent threshold k for an appropriate comparison is indicated in the table. MNI coordinates, peak activation, and volume are given along with the significance threshold estimate. L-left, R-right hemisphere.

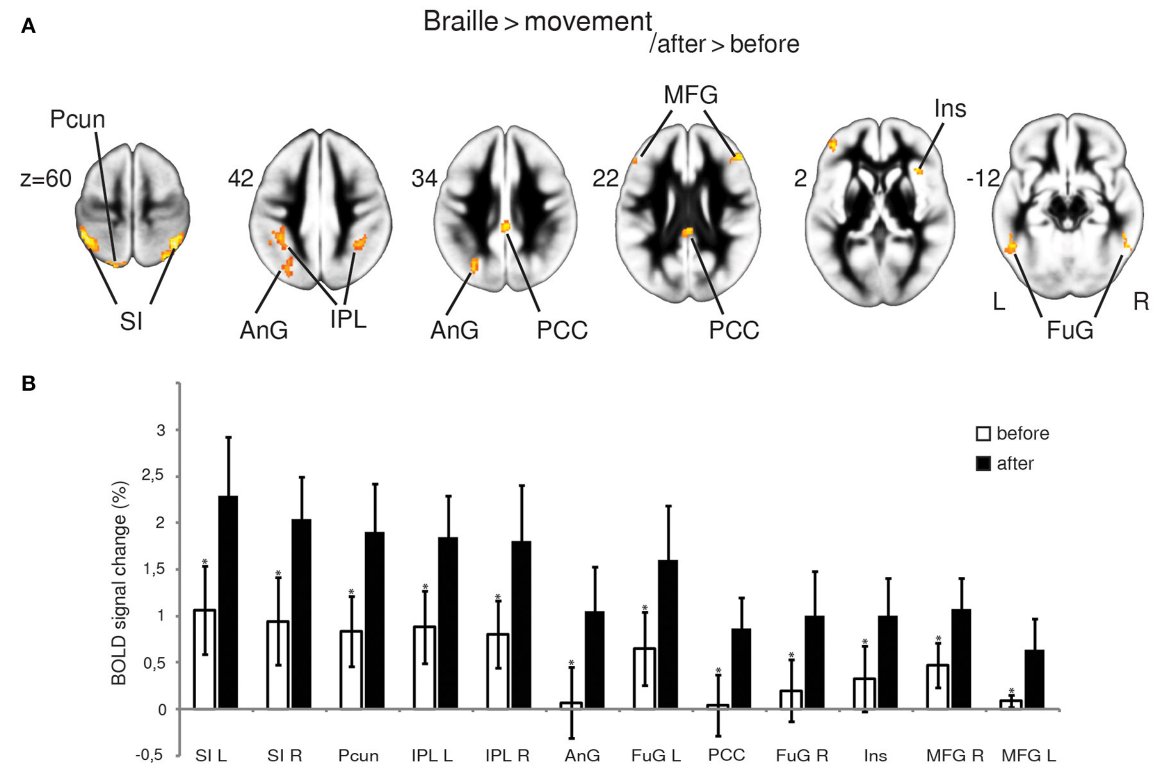

FIGURE 2 | fMRI results. Statistical parametric maps of the functional plasticity induced by Braille training revealed by Braille > movement after vs. before training comparison, FWE corrected at $p < 0.05$ **(A)**; percentage of BOLD signal change **(B)**. Percentage of signal change was calculated individually within a spherical volume of interest with a diameter of 10 mm (*$p < 0.05$, paired *t*-test). Abbreviations: AnG—angular gyrus, FuG—fusiform gyrus, Ins—insula, IPL—inferior parietal lobule, MFG—medial frontal gyrus, PCC—posterior cingulate cortex, Pcun—precuneus, SI—primary somatosensory cortex, L—left, R—right.

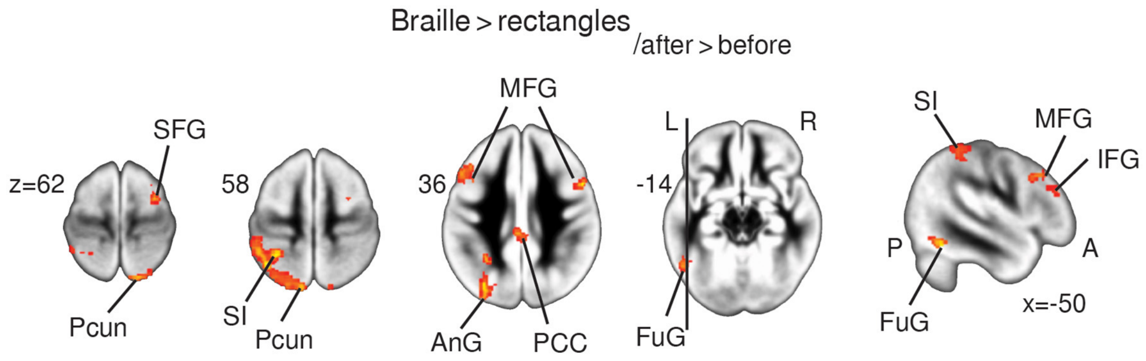

FIGURE 3 | fMRI results. Statistical parametric maps of functional plasticity induced by Braille training. Results from Braille > rectangles $_{\text{after > before}}$ comparisons are presented on the axial slices of the gray matter template (MNI). FWE corrected at $p < 0.05$. Abbreviations: AnG—angular gyrus, FuG—fusiform gyrus, IFG—inferior frontal gyrus, Ins—insula, LinG—lingual gyrus, MFG—medial frontal gyrus, PCC—posterior cingulate cortex, Pcun—precuneus, SFG—superior frontal gyrus, SI—primary somatosensory cortex.

lobule. Other areas of increased activation were located within posterior cingulate cortex, the middle frontal gyrus, and the fusiform gyrus bilaterally, as well as in the right insula (**Figure 2A**). The strength of the BOLD signal change among structures revealed by this comparison is shown in **Figure 2B**.

Braille Characters Discrimination Task > Rectangles $_{\text{after > before}}$

The Braille vs. rectangles comparison was constructed to isolate the specific effect of Braille character processing as a higher order cognitive task, by subtracting the activation by the same finger movement but crucially without the letter-related connotations.

TABLE 2 | Changes in FA maps after Braille training.

$k = 26$	x	y	l		cluster	T	%
Parietal Operculum WM (SII)	−42	−32	26	L	204	7.15	+1.7
	−40	−32	16	L		6.93	
	−40	−16	20	L		6.80	
Postcentral Gyrus WM (SI)	−36	−28	46	L	126	6.28	+2.3
	−38	−36	60	L		5.81	
	−44	−30	56	L		4.89	
Lingual Gyrus WM	16	−84	−10	R	93	7.50	+1.61
	26	−92	−14	R		7.43	
Superior Frontal Gyrus WM	12	12	70	R	85	5.88	+1.65
	14	12	62	R		5.42	
Lingual Gyrus WM	−26	−84	−4	L	76	9.27	+1.8
	−34	−86	−10	L		7.40	
Parahippocampal Gyrus WM	−28	−32	−18	L	75	5.27	+1.5
	−34	−44	−26	L		5.20	
Fusiform Gyrus WM	28	−54	−8	R	62	8.04	+1.1
Middle Frontal Gyrus WM	42	0	58	R	49	6.71	+1.2
	34	−4	62	R		4.67	
Superior Frontal Gyrus WM	−10	−8	56	L	36	9.61	+2.25
	−16	−12	64	L		4.08	
Inferior Frontal Gyrus WM	46	22	−6	R	36	5.87	+1.51
Lingual Gyrus WM	−14	−52	0	L	34	6.25	+1.42
Superior Frontal Gyrus WM	−24	8	70	L	30	5.68	+1.3
	−16	12	72	L		5.35	
Thalamus LP	−14	−22	10	L	27	6.99	+1.8
	−16	−24	18	L		4.58	

MNI coordinates, peak activation, and volume percentage of FA change are given along with the significance threshold estimate. Results revealed by paired t-test between the FA maps before and after the training. SI—primary somatosensory cortex, SII—secondary somatosensory cortex, LP—lateral-posterior; L—left, R—right hemisphere. T-values of the peak activations, $p < 0.05$ (correction for multiple comparisons at cluster level, Family Wise Error), and extent threshold k for an appropriate comparison is indicated in the table.

Results depicted a stronger response bilaterally within the precuneus, the posterior, and anterior cingulate cortex, as well as the middle and inferior frontal gyri. Left-lateralized changes in BOLD signal were found within the fusiform and angular gyrus, as well as in primary somatosensory finger representation within the postcentral gyrus (**Figure 3**).

ROI Analysis of Parietal Operculum/SII

Since the whole-brain analysis did not reveal functional changes within the secondary somatosensory cortex, we decided to conduct additional ROI analyses. Two ROI's were created, for each left and right SII, using group data from the Braille discrimination task > finger movement contrast from both sessions (**Figure 4A**) and coordinates from our previous study (**Figure 4B**) revealed by the Braille discrimination task > rest comparison (Debowska et al., 2013). Parameter estimates for Braille and rectangles conditions were calculated individually within a spherical region-of-interest with a diameter of 6 mm. Interaction effects were tested using random-effects analysis, with results showing no significant differences in SII activity before and after the training in both the Braille or rectangles discrimination tasks (**Figure 4**). Based on these results, we conclude that there is no evidence for functional plasticity within the SII attributed to short-term Braille learning.

DTI Results

Voxel-wise comparison of the FA maps before and after the Braille training revealed a set of the white matter regions in which FA changed as a result of tactile learning. FA was increased among the crucial areas of the somatosensory pathway: the postcentral gyrus (SI), the parietal operculum (SII), and the lateral posterior/pulvinar thalamic nuclei of the left hemisphere (**Figure 5A**). Other changes were located within frontal and parietal-occipital areas: the right inferior and medial frontal gyri, the superior frontal gyrus, fusiform gyrus, and lingual gyrus bilaterally, and the left parahippocampal gyrus (**Figure 5B**). The opposite comparisons (before > after) of the FA maps did not reach statistical significance. The full set of obtained results along with the statistics and percentage of FA change is given in **Table 2**.

DISCUSSION

Relatively short but intensive tactile training based on Braille reading induced modifications in both primary somatosensory and higher ordered areas. We observed BOLD signal changes

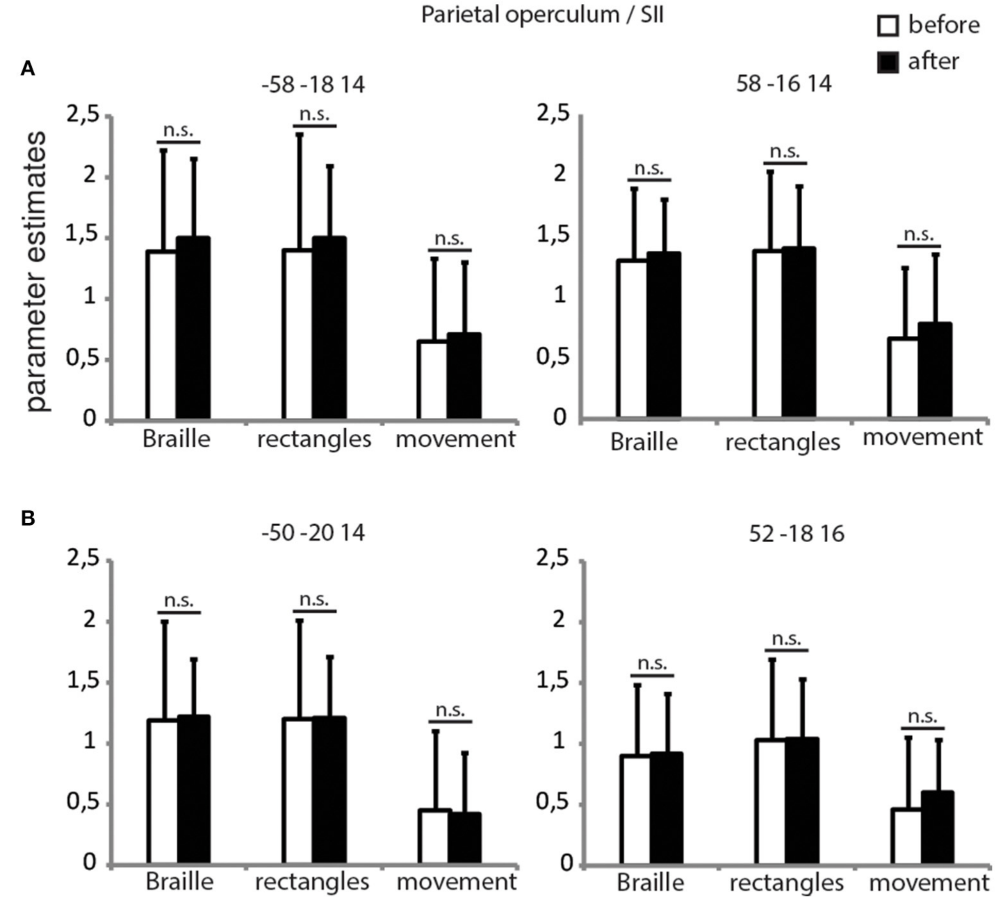

FIGURE 4 | ROI's for parietal operculum/SII. Parameter estimates for all of the experimental conditions before and after the training in the secondary somatosensory cortex bilaterally. Coordinates for creating 6 mm spheres were chosen on the basis of our current **(A)** and previous study **(B)**. *p* <0.05, corrected for multiple comparisons.

likely associated with increased synaptic strength, excitability and expansion in local synaptic connectivity (Saar and Barkai, 2009; Wu and Mel, 2009; Bekisz et al., 2010; Froemke et al., 2013; Jasinska et al., 2013). With DTI, we found increases in the fractional anisotrphy index, likely reflecting strengthening of the intra-cortical connections in response to the demand of increased communication during new-skill acquisition (Blumenfeld-Katzir et al., 2011; Sampaio-Baptista et al., 2004). Changes in fMRI activation were congruent with changes in FA within both somatosensory and inferior occiptiotemporal cortices. The simultaneous use of both methods allows a more precise assessment of task-related plasticity. Its exact impact on relevant brain regions is discussed below.

Tactile Training—The Somatosensory Pathway

SI. Since Braille reading as a tactile activity must engage somatosensory processing, we expected to find alteration in cortical response and white matter structure within the somatosensory pathway. The contrast of Braille character discrimination vs. finger movement revealed areas that responded stronger to swiping fingers over Braille dots relative to swiping fingers without touching the surface, thus, finger movement acted as a motor control. Following training, the strongest activation increase observed for this contrast was found in the SI (**Figures 2A,B**) bilaterally. The primary somatosensory cortex was previously reported to manifest mainly contralateral responsiveness (Hari et al., 1993; Deuchert et al., 2002; Hlushchuk and Hari, 2006) and several more recent papers have reported its bilateral involvement in somatosensory information processing (Blatow et al., 2007; Tamè et al., 2012; Chung et al., 2014). The current study reports robust bilateral activation of the primary somatosensory representation during a tactile discrimination task before and—even stronger—after the training. We suggest that this may be a result of increased interhemispheric communication between homotopic regions related to the task complexity and top-down attention (Verstynen et al., 2005; Perez and Cohen, 2008).

In parallel with change in the magnitude of the BOLD signal, we found FA increases within the postcentral gyrus in the region

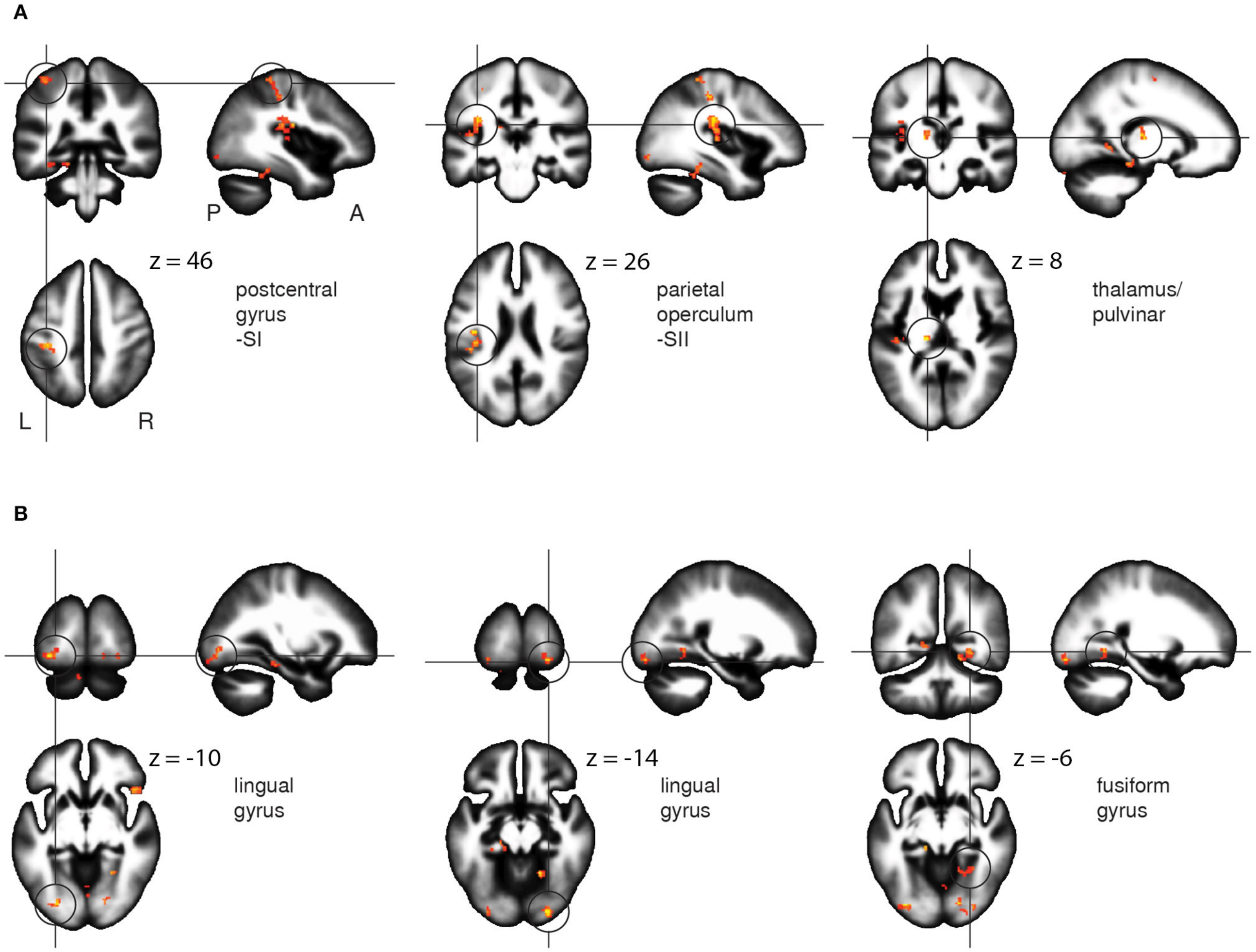

FIGURE 5 | FA results. White matter areas showing an increase of fractional anisotropy as a result of the Braille training, within somatosensory (A) and the ventral stream (B) regions. Results revealed by paired *t*-test between the FA maps before and after the training. Statistics presented on the sagittal (x), coronal (y), and axial (z) slices of the white matter tissue template (MNI). FWE corrected at $p < 0.05$, $k = 26$.

corresponding to the functional localization of the contralateral finger representation within the SI. The increase of activation and in white matter integrity within the SI (**Figure 5A**) provides strong evidence for the SI's specific engagement in Braille reading skill acquisition. These results are in line with previous findings concerning plasticity of the primary somatosensory representation induced by both short and long-term tactile training (Pascual-Leone and Torres, 1993; Pleger et al., 2003; Hodzic et al., 2004). The increase of white matter integrity around the altered functional SI representation documents structural plasticity as a novel aspect of learning-induced SI modification.

Interestingly, our results are contrary to those recently presented by Sathian et al. (2013), where no effect of tactile learning was found within the SI. We propose that this might be caused by key differences in the experimental procedure—our subjects were trained to actively discriminate different spatial patterns with assigned meaning (Braille characters), subjects in Sathian's study were trained in pure perceptual learning (micro-spatial task based on a linear three-dot array), and the touch was passive. There are also differences in training duration (fixed vs. individual performance criterion), stimuli presentation protocols (active in our study vs. passive) and duration (3 s per pair in event-related design vs. 1 s per single stimulus presented in block-design).

Our results are also divergent from those of Siuda-Krzywicka et al. (2016) who trained sighted subjects in whole-word tactile reading for 9 months. After such a long period of training, Siuda-Krzywicka et al. (2016) did not find changes in the somatosensory cortex. Instead, their results showed an increase in the left fusiform gyrus activation (Visual Word Form Area, VWFA), where most likely this divergence is due to the very long learning period (9 months vs. 3 weeks) and the complexity of stimuli used (whole words vs. pairs of Braille characters). Experiments that study learning-related plasticity at multiple time points (Lövdén et al., 2013) suggest that at the initial stage of Braille learning described by Siuda-Krzywicka et al. (2016), the somatosensory cortex might have increased its response to Braille words, and as the effects of early sensory learning consolidated in the somatosensory cortex, the cortical focus of learning might have shifted elsewhere—to the ventral visual stream.

Parietal Operculum/SII

We found no functional changes in either ipsi- or contralateral SII, but a highly significant FA increase within white matter in the parietal operculum (anatomical localization of the SII) contralateral to the reading finger (Eickhoff et al., 2010). The changes in white matter structure clearly suggest functional involvement of the contralateral SII in acquisition of the new tactile ability, whereas the absence of increased functional activation after 3 weeks of training raises questions regarding the precise character of this involvement. The importance of the SII in tactile processing, including Braille characters' discrimination in sighted individuals (Sadato et al., 2002), is well documented and we see its strong activation during the Braille character discrimination task used in the present study (**Figure 4**). We propose that lack of the increase in activation of the SII following training might be due to the rigid timeframe used for training. In other words, we speculate that if checked at different (shorter) time points, e.g., a few days after onset of training, the SII might demonstrate its plasticity in terms of functional involvement—stronger at the beginning of training and coming back to normal when the skill became easier (Pleger et al., 2003; Vahdat et al., 2014) and when the white matter tracts are already remodeled. An alternative interpretation is that SII is not involved into neuroplasticity indcued by training, but only play its usual role in 'transmitting' information to brain regions involved in stimuli processing.

Additionally, the lack of long-term functional change in SII while increased activity was observed in the SI cortex might inform an ongoing discussion about hierarchical vs. parallel information processing between the SI and SII (Chung et al., 2014; Klinger et al., 2015). While early animal studies suggested strict dependencies between the SI and SII cortices by demonstrating the extinction of the SII activity after lesioned within SII (Pons et al., 1988), it was later proposed that SII may process sensory information independently (Zhang et al., 2001). In humans, effective connectivity studies showed information flow relating to texture, from the SI to the parietal operculum (Sathian et al., 2011). Here, if increased activity in the SI does not alter the activity within the SII, it is most likely that the SII reacts independently and is not a simple reflection of the SI. Another possible explanation is that although the SII is necessary in tactile stimuli processing, its role in the well-trained tactile pattern discrimination task is no longer needed because of the altered global brain pattern of activity and stronger engagement of regions specified in the object recognition—FuG (**Figure 2**; **Table 1**). The FA increase observed within areas of the parietal operculum might then reflect an enhanced intra-cortical communication occurring while mastering the new tactile recognition task.

Outside of the Somatosensory Domain: Fronto-Parietal Cortex and the Ventral Stream

As Braille characters become meaningful to the subjects as a result of training, it should be possible to determine loci where this meaning is extracted. Although the task in the scanner required only a same/different answer, activation of the brain was strongly affected by the meaning of the discriminanda. When we computed the interaction of Braille > rectangles with the difference between the before- and after- training scans, we found activations in the left fusiform cortex, medial and inferior frontal gyri, and the angular gyrus (**Figure 3**, **Table 1**). Increased activation of those areas after training might be language related, since they were found at locations typical to those found in readers of a variety of different scripts (Perfetti et al., 2010; Szwed et al., 2014). Increased activity within ventral stream activation suggest that even short-term tactile Braille reading training may result in activation of brain regions involved in categories recognition (Tyler et al., 2013), which might be interpreted as a having semantic conotations. Alternatively, they might be task-related. Unfortunately, we do not have more appropriate behavioral nor imaging data to discriminate between those two.

The increase in activity within the fusiform gyrus (**Figure 3**, **Table 1**) is congruent with previously reported involvement of the lateral occipital cortex/fusiform gyrus in tactile object recognition in both blind and sighted subjects (Sadato et al., 2002; Amedi et al., 2003; Striem-Amit et al., 2012) or multisensory object perception (Kassuba et al., 2011, 2014; Schlaffke et al., 2015). Alternatively, it could reflect the emergence of tactile Braille recognition mechanisms similar to those found in the VWFA (Price and Devlin, 2001; Cohen et al., 2002; Dehaene and Cohen, 2011), recently found in sighted whole-word tactile Braille readers (Siuda-Krzywicka et al., 2016). Interestingly, these fMRI results were accompanied in our study by FA increase in the lingual gyrus bilaterally and within the fusiform gyri (**Figure 2**, **Table 2**). Our results might thus constitute the first report of white matter integrity changes within higher-ordered and visual areas induced by short-term tactile training in sighted subjects. Apparently even short-term tactile Braille reading training may result in activation of brain regions involved in language in general and specifically—in reading.

Finally, some of our results (FuG, AnG, PCC, Pcun) have much in common with those observed after Morse code deciphering training using auditory stimuli (Schmidt-Wilcke et al., 2010). Our results not only support these findings, but also complement them with a novel aspect, showing significant white matter changes throughout the network involved in acquisition and usage of alphabet signs perceived by a different (somatosensory) sensory modality.

CONCLUSION

Short-term tactile training based on Braille reading increased SI activation, confirming the presence of learning-induced plasticity in the primary somatosensory cortex. No functional effects were found within secondary somatosensory cortex, however FA increase within the parietal operculum suggest that the SII was involved in acquisition of this new sensory skill, and an fMRI measurement at a third time point might have captured a change of BOLD activity also in the SII. Increased activation of the fusiform gyrus followed by structural alteration in white matter of occipital regions demonstrates that a relatively short tactile training can induce plastic changes in the ventral visual cortex. In summary, our study shows how acquisition and mastering tactile discrimination tasks induce modifications in the pattern and intensity of brain activation and white matter integrity of somatosensory areas, higher-ordered pathways and in the thalamus.

LIMITATIONS

Our training has been arbitrary set for a fixed period of time. It would be extremely interesting and informative to conduct longitudinal study with multiple scanning time points (week by week or even day by day) as well as follow up study to determine how long the observed changes persists. More detailed imaging sequences such as spectroscopy might also brought better insight in to the neurobiological underpinnings of the plastic changes. Moreover, since whole-brain analyses of diffusion indices are of several limitations including Partial Volume Effects and EPI distortions, and requires perfect co-registration (Beaulieu, 2002), other analyses such as tractography combined with i.e., computational anatomy (Draganski et al., 2014) would shed some more light on the exact localization of the reorganized tissue and allow for a better insight into nature of neuroplasticity.

AUTHOR CONTRIBUTIONS

Study conception and design: WD, AN, MS, MK. Acquisition of data: WD, TW, AK. Analysis and interpretation of data: WD, TW, MK. Drafting of manuscript: WD, AN, MK. Critical revision: WD, MS, AN, MK.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2016.00460

Figure S1 | Braille training—overall fMRI results. Statistical parametric maps of the Braille vs. movement **(A)** and Braille vs. rectangles **(B)** contrasts, separately for before and after the Braille training. Results are presented on a glass-brain in MNI space (view from the top, back, and left of the brain), $p < 0.05$, FWE.

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The Neural Correlates of Grasping in Left-Handers: When Handedness Does Not Matter

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Neurophysiological studies showed that in macaques, grasp-related visuomotor transformations are supported by a circuit involving the anterior part of the intraparietal sulcus, the ventral and the dorsal region of the premotor area. In humans, a similar grasp-related circuit has been revealed by means of neuroimaging techniques. However, the majority of "human" studies considered movements performed by right-handers only, leaving open the question of whether the dynamics underlying motor control during grasping is simply reversed in left-handers with respect to right-handers or not. To address this question, a group of left-handed participants has been scanned with functional magnetic resonance imaging while performing a precision grasping task with the left or the right hand. Dynamic causal modeling was used to assess how brain regions of the two hemispheres contribute to grasping execution and whether the intra- and inter-hemispheric connectivity is modulated by the choice of the performing hand. Results showed enhanced inter-hemispheric connectivity between anterior intraparietal and dorsal premotor cortices during grasping execution with the left dominant hand (LDH) (e.g., right hemisphere) compared to the right (e.g., left hemisphere). These findings suggest that that the left hand, although dominant and theoretically more skilled in left handers, might need additional resources in terms of the visuomotor control and on-line monitoring to accomplish a precision grasping movement. The results are discussed in light of theories on the modulation of parieto-frontal networks during the execution of prehensile movements, providing novel evidence supporting the hypothesis of a handedness-independent specialization of the left hemisphere in visuomotor control.

Keywords: reach-to-grasp, handedness, left-handers, functional magnetic resonance imaging, dynamic causal modeling

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INTRODUCTION

The neural correlates of grasping in humans have been intensively investigated by means of neuroimaging and brain stimulation techniques (for reviews see Castiello, 2005; Castiello and Begliomini, 2008; Filimon, 2010). These studies mainly rely on neurophysiological findings in the attempt to identify in humans a cortical network similar to that described in monkeys, in which the anterior intraparietal area (AIP), the ventral (F5), and the dorsal (F2) premotor cortices play a key role for the execution of grasping movements (Murata et al., 1997; Rizzolatti and Luppino, 2001; Raos et al., 2004; see Castiello, 2005; Castiello and Begliomini, 2008 for reviews). The majority of these studies highlighted that grasping actions performed with one hand or the other are usually mirrored by an asymmetric recruitment of the two hemispheres in functional terms (left hand/right hemisphere vs. right hand/left hemisphere) (Brouwer et al., 2001; Johnson-Frey et al., 2005; Basso et al., 2006; Pollok et al., 2006; Begliomini et al., 2008; Martin et al., 2011; Kourtis et al., 2014). However, in some cases ipsilateral activations within motor-related areas have also been reported (Kim et al., 1993; Volkmann et al., 1998; Baraldi et al., 1999; Kobayashi et al., 2003; Verstynen et al., 2005).

To date, most of these neuroimaging studies have focused on right-handed participants performing grasping movements with their right hand, neglecting a basic feature of the human body and motor behavior: the presence of two functional hands, physically symmetrical but functionally distinct. It has been estimated that 90% of humans show the tendency to use their right hand for interacting with objects and the environment, while the left hand plays a supporting role. However, the remaining 10% of the population shows the opposite functional pattern with the left hand as a dominant one (Perelle and Ehrman, 1994). Whether the mechanisms underlying the motor control of the left-handers simply mirror that of the right-handers has been the focus of behavioral studies. In general, these studies simply observe whether there is a tendency, in both right- and left-handers, to choose a particular hand to perform a given motor task, such as grasping (Gonzalez et al., 2006, 2007; Gonzalez and Goodale, 2009; Stone et al., 2013; Main and Carey, 2014; Stone and Gonzalez, 2015). Overall, these studies indicate the left hemisphere/right hand ensemble as specialized for grasping, independently from handedness, and the right hemisphere/left hand ensemble as critical in haptic tasks (Stone et al., 2013; Stone and Gonzalez, 2015). What is less well understood is how the human brain controls grasping movements with the right or the left hand, in both right- and left-handers, as there are only a few imaging studies focusing on this issue. An unpublished report (Culham et al., unpublished) considered right-handers performing grasping movements with either the right or the left hand toward 3D targets while being scanned. These results indicated that grasping with either hand recruits AIP bilaterally, with a significantly stronger and more extended recruitment of the hemisphere contralateral to the hand used. Similar evidence has been provided also by Martin et al. (2011) and very recently also by Tzourio-Mazoyer et al. (2015): both studies show that while right-handers are characterized by a clear asymmetric pattern of brain activity (left hemisphere/right hand; right hemisphere/left hand), left-handers show a bilateral recruitment of brain regions involved in motor control, independently of the hand used. In another study (Begliomini et al., 2008) right- and left-handers were scanned while performing a precision grip task with the right or the left hand. Results confirmed the crucial role of the bilateral AIP: this region, together with the right dorsal premotor cortex (dPMC) and the right cerebellum appeared to be significantly modulated by hand and handedness, in both right- and left-handers. The fact that both AIPs and the cerebellum showed a similar pattern of modulation according to the hand and handedness provided support to the existence of a cerebellum-AIP connections in humans, as already described in monkeys (Clower et al., 2005). Effective connectivity approach (Dynamical Causal Modeling—DCM; Friston et al., 2003) was recently adopted to further test the idea that in right-handers the contribution of the two hemispheres to the execution of grasping movements might vary according to the performing hand (Begliomini et al., 2015). The results highlighted strengthened inter-hemispheric connections between dPMCs during grasping with the left non-dominant hand and further emphasized the fundamental contribution of the dPMC in monitoring the fingers' configuration, suggesting that when the less skilled hand is used, additional control is required.

For the first time here we explore the contribution of both hemispheres to the execution of a precision grasping task, performed by left-handers with the left or the right hand. Specifically, we aim to observe (i) whether the execution of a precise grasp involves the grasping network according to a specular schema, so that grasping with the left dominant hand (LDH) mainly recruits the right hemisphere, whereas grasping with the right non-dominant hand (RNH) mainly recruits the left hemisphere; and (ii) whether left hand dominance influences intra-hemispheric connectivity patterns among areas belonging to the grasping circuit, as observed in a previous study in right handers (Begliomini et al., 2015). Relying on structural and functional evidence obtained in both humans and monkeys (see **Table 1**) (iii) we also investigated whether inter-hemispheric effective connectivity between homologous areas could be affected either by the use of the right hand, which is non-dominant in left-handers, or rather by the use of the left hand, which is supposed to be dominant, but potentially less-skilled. We considered the four key regions of the "grasping network," namely the AIP, the ventral premotor cortex—vPMC, dPMC and the primary motor cortex—M1 (Castiello and Begliomini, 2008), hypothesizing that connections between homologous areas of the two hemispheres would be modulated during precision grasping task, according to the performing hand. In this respect, three possible scenarios were considered (**Figure 1**):

TABLE 1 | Studies demonstrating the existence of inter-hemispheric connections between grasping areas considered in the present study.

Connection	Non-human primate studies	Human primate studies
AIP—AIP		Culham and Valyear, 2006; Begliomini et al., 2008; Le et al., 2014; Tunik et al., 2005; Rice et al., 2006; Davare et al., 2007
vPMC—vPMC	Boussaoud, 1995; Dancause et al., 2007	
dPMC—dPMC	Marconi et al., 2003	Begliomini et al., 2008, 2015
M1—M1	Jenny, 1979; Leichnetz, 1986; Rouiller et al., 1994	Davare et al., 2007

AIP, Anterior IntraParietal; vPMC, ventral PreMotor Cortex; dPMC, dorsal PreMotor Cortex; M1, Primary Motor Cortex.

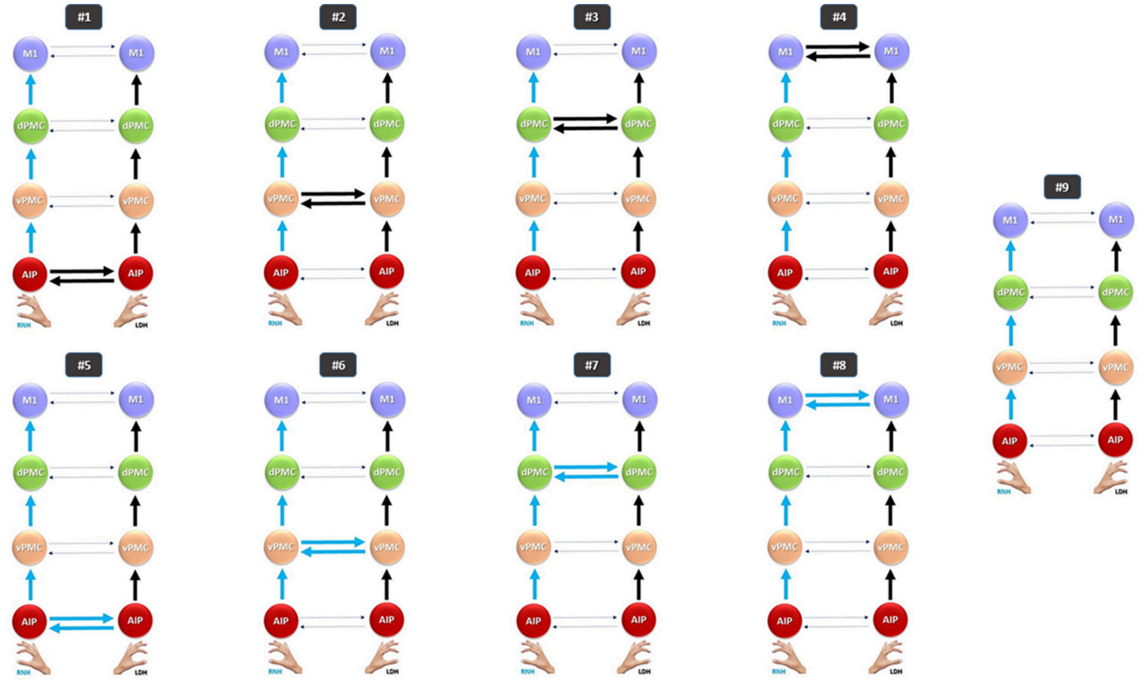

FIGURE 1 | Models tested for the RFX Bayesian Model Selection (BMS). Models #1–4 belong to the LDH family; models #5–8 refer to the RNH family; model #9 (null model) does not belong to any "family" and does not include any inter-hemispheric connection. Solid blue arrows indicate connections (both intra- and inter-hemispheric) modulated by Precision Grip movements performed with the RNH; solid black arrows indicate connections modulated by PG movements performed with the LDH; dotted arrows indicate connections not affected by modulation effects. AIP, Anterior Intraparietal; vPMC, Ventral Premotor Cortex; dPMC, Dorsal Premotor Cortex; M1, Primary Motor Cortex; LH, Left Hemisphere; RH, Right Hemisphere; RNH, Right Non Dominant Hand; LDH, Left Dominant Hand.

(1) The execution of precision grasping with the LDH modulates contralateral intra-hemispheric *and* inter-hemispheric connections between homologs areas (models #1–4);

(2) The execution of precision grasping with the RNH modulates contralateral intra-hemispheric *and* inter-hemispheric connections between homologs areas (models #5–8);

(3) The execution of precision grasping with either the LDH or the RNH modulates contralateral intra-hemispheric but *not* inter-hemispheric connections between homologs areas (model #9).

METHODS

Participants

Sixteen participants (11 females; age range: 21–32 years; mean age: 26.1 years) participated in the experiment. All participants had normal vision and had no history of neurological, psychiatric or motor disease. Left hand dominance was evaluated by means of the Edinburgh Handedness Inventory (Oldfield, 1971), and only participants with a laterality score index ranging from 0.6 to 1 (strongly left-handed) were included. Before undergoing the fMRI session all participants underwent a safety screening and received all relevant information about the experimental procedure and data treatment. The study was carried out according to the guidelines of the Ethics Committee for Clinical Practice of Padova University Hospital. All participants gave written informed consent in accordance with the Declaration of Helsinki. The study has been supported by a grand awarded from the Italian Ministry for Education, University and Research to Chiara Begliomini (CPDA117759/11).

Experimental Stimulus

The stimulus was a spherical MR-compatible object of 3 cm diameter, presented at a distance allowing the comfortable execution of a grasping movement, and which was the same for both hands. A regular geometric shape was chosen to allow for comparisons with previous neurophysiological (Gallese et al., 1994; Umilta et al., 2007) and neuroimaging (e.g., Begliomini et al., 2007a) studies. Stimulus dimension was selected in order to elicit a precision grip, that is the opposition of thumb and index finger. This kind of prehensile action has been well described in humans at both neural (Ehrsson et al., 2001; Frey et al., 2005; Culham and Valyear, 2006; Begliomini et al., 2007b, 2014; Turella and Lingnau, 2014) and behavioral level (e.g., Jeannerod, 1981, 1984; Castiello et al., 1993; Savelsbergh et al., 1996; Cuijpers et al., 2004; see Smeets and Brenner, 1999 for a review). In addition, neuroimaging studies have highlighted how planning and execution of precision grip movements are characterized by a larger involvement of the fronto-parietal network with respect to other types of grasping (e.g., whole hand grasp – Begliomini et al., 2007a,b; see Filimon, 2010 for a review).

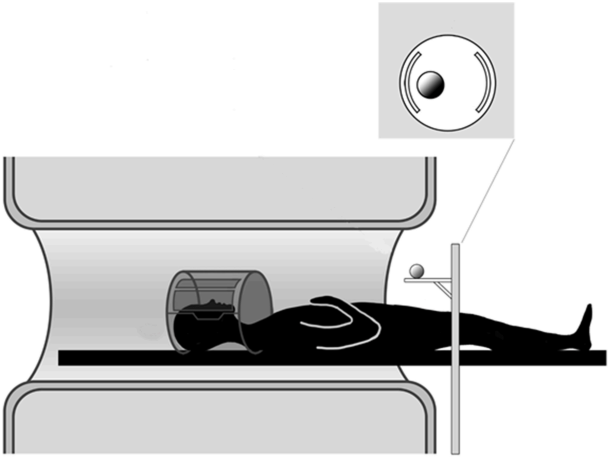

FIGURE 2 | Experimental setup. The participant is lying in the MR scanner bore and the platform allows the presentation of a stimulus at a comfortable distance. A pillow, slightly tilting the head, allows for a direct viewing of the stimulus.

Experimental Setup

The stimulus was presented on a small circular MR compatible table (**Figure 2**). Participants' upper arms were kept still and tight to the body with an elastic band as to minimize possible head motion induced by arm movements. In order to ensure a consistent starting position for both hands and comparable for both hands, all participants wore a plastic belt with a pad in the middle (e.g., on the body midline). They were instructed to keep both hands placed on the pad in a relaxed position with the palms facing down between trials. The participants' head was supported by a foam pillow, in order to have a ~30° tilted position, to allow for a direct view of the stimuli without mirrors (Culham et al., 2003; Cavina-Pratesi et al., 2007).

Task Procedures

The participants were instructed to perform a grasping movement toward the stimulus at a natural speed, without any time restraint, using a precision grip with either the LDH or the RNH hand according to a sound delivered by means of pneumatic MR-compatible headphones (right hand: low pitch - duration: 200 ms; frequency: 1,7 kHz; left hand: high pitch - duration: 200 ms; frequency: 210 Hz). Although the stimulus was constantly visible, participants were instructed not to begin the movement until after hearing the sound. An operator monitored the entire experiment from the control room, checking that the task was performed correctly. Participants were explicitly instructed to look at the object throughout action execution.

Experimental Design

The experiment adopted a mixed event-related design, with performing hand (LDH, RNH) manipulated as within-subjects factor (within runs). Trials involving the same hand were gathered in sequences varying from four to eight elements, as to minimize task-switching related brain activity, induced by frequent changes of the effector (Culham et al., 2003). Inter-stimulus interval (ISI) was randomized across trials, varying from 3 to 8 s according to a "long exponential" probability distribution (Hagberg et al., 2001). The whole experiment consisted of 120 trials (60 per hand), divided into 2 runs of 60 trials each.

Imaging Parameters

Images were acquired by means of a 1.5 Tesla scanner (Siemens Avanto) with a standard 8-channels coil. Functional images measuring the blood oxygenation level-dependent (BOLD) contrast were acquired with a gradient-echo, echo-planar (EPI) T2*-weighted sequence covering the whole brain volume (37 continuous axial slices, descending order, 56×64 voxels, $3\,\text{mm} \times 3\,\text{mm} \times 3.3\,\text{mm}$ resolution, FOV $= 196\,\text{mm} \times 224\,\text{mm}$, flip angle $= 90°$, TE $= 49$ ms). 114 volumes were acquired for each of the two runs (5 min and 42 s for each run, for a total acquisition time of 11 min and 24 s). A high-resolution structural T1-weighted image was acquired for each participant (3DMP-RAGE, 176 axial slices, 1 mm isotropic voxel, no interslice gap, data matrix 256×256, TR $=$ 1,900 ms, TE $= 2.91$ ms, flip angle $= 15°$).

Data Analysis

Data Preprocessing

Functional data underwent spatial pre-processing and analysis with the SPM (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm), version 12. The first four scans of each functional run were excluded from data analysis to allow for T1 equilibrium state. For each participant, the time series were temporally realigned to the middle slice and were corrected for head motion (translations/rotations), taking the first volume of the series as a reference. The structural image was then co-registered to the mean of all functional images previously corrected for signal intensity inhomogeneities. Functional images were then normalized according to the MNI152 template (Montreal Neurological Institute, http://www.mni.mcgill.ca) implemented in the software SPM12, and were finally smoothed using a $6 \times 6 \times 6.6$ mm FWHM 3D Gaussian kernel (twice the native voxel size).

General Linear Model

At the first level, for each participant, movements performed either with the LDH or the RNH were modeled as single events with an assumed duration of about 1.5 s on the basis of behavioral observations preceding the experimental session (this was done to allow the participants become familiar with the experimental setup). Trials timing was defined on the basis of the onset of the cueing sound indicating the hand to be used to perform the grasping action. Movements performed with either the LDH or the RNH were modeled as separate regressors, and were convolved with a canonical, synthetic HRF (haemodynamic response function) to produce individual models (Henson, 2001). A General Linear Model (Holmes et al., 1997) was run for each single subject, including the two regressors of interest (LDH; RNH) plus additional regressors of no interests (head motion parameters created during the realignment stage; trials for which the participants did not react/did not perform the movement correctly). The functional time series were concatenated over the two sessions, and two additional regressors of no interest were added to the model to account for possible session effects.

DCM Models

The aim of DCM (Friston et al., 2003; Stephan et al., 2007) is to identifying possible causal relationship among brain regions through the comparison of several different causality hypotheses (e.g., models) involving a given pool of a priori identified brain regions. In the present study, this approach was adopted to characterize how the two hemispheres of a group of left-handed participants contribute to the execution of a precision grasping movement performed with the LDH or the RNH. Effective connectivity between areas belonging to the grasping circuit in humans was explored, hypothesizing nine different scenarios (**Figure 1**). The considered regions are: AIP, vPMC, dPMC, and M1 (Castiello, 2005; Castiello and Begliomini, 2008; Filimon, 2010). Here the basic idea eas that the performing hand (LDH or RNH) could modulate causal connections between homologous areas of the two hemispheres (e.g., right M1-left M1) according to the models described in **Figure 1**. First, *intra-hemispheric* connections among the grasping key regions (AIP, vPMC, dPMC, and M1) were considered, according to the results obtained by single cell recordings performed on macaques (see **Table 1**) and relying on the model described by Castiello and Begliomini (2008). This first step was performed to confirm the involvement of the right hemisphere in coding for grasping performed with the LDH and the left hemisphere in coding for grasping performed with the RNH as a starting point. Second, *inter-hemispheric* connections between homologous areas in the two hemispheres were explored. Concerning this step, it has to be emphasized that previous neurophysiological data represented the main reference point for connections between dPMC, vPMC, and M1. For AIP we mainly relied on the neuroimaging (Culham et al., 2006; Begliomini et al., 2008, 2015) and neurostimulation results (Tunik et al., 2005; Rice et al., 2006; Le et al., 2014) previously reported in humans. Overall these studies agree that a bilateral recruitment of the AIP is crucial for grasping execution. For all participants nine different models were considered, assuming nine different connectivity hypotheses (see **Figure 1**). Anatomical *context-independent* models (DCM-A matrix) were formulated on the basis of the abovementioned literature and the performing hand was adopted as a *context-dependent* modulatory agent on the forward connections (LDH; RNH—DCM-B matrix). AIP was included as a driving input (matrix C) for both hemispheres since the visuomotor analysis of the object target of the action represents an essential requirement for the successful accomplishment of a grasping action. In this sense, both neurophysiological and neuroimaging support the consideration of AIP as a crucial region (Binkofski et al., 1998, 1999; Castiello, 2005; Frey et al., 2005; Rice et al., 2006, 2007; Begliomini et al., 2007b; Castiello and Begliomini, 2008): for this reason. Any possible hypothesis related to stimulus-response coupling mechanism (sound → performing hand) was not taken into account, since the present study was focused on grasping execution, rather than previous stages such as planning. According to the model (envisaged by Castiello and Begliomini, 2008), the modulation induced by the act of performing a precision grasp is supposed to spread through ipsilateral connections from AIP to vPMC, and from vPMC to dPMC. The following connection is supposed to link dPMC with M1, which is assumed to be the last step of the considered models (see **Figure 1**). Models #1–4 were considered as belonging to the "LDH" family, given their assumption of inter-hemispheric interactions between homologous grasping areas as modulated by precision grip movements performed with the LDH (model #1: right AIP ↔ left AIP; model #2: right vPMC ↔ left vPMC; model #3: right dPMC ↔ left dPMC; model #4: right M1 ↔ left M1). Models #5–8 hypothesize the same architecture, but assume that inter-hemispherical connections between homologous areas are influenced by precision grip movements performed with the RNH ("RNH" family; model #5: left AIP ↔ right AIP; model #6: left vPMC ↔ right vPMC; model #7: left dPMC ↔ right dPMC; model #8: left M1 ↔ right M1). The "null" model hypothesized no inter-hemispheric connection between the two hemispheres (#9), to test the possibility that the hemispheres do not interact with each other while performing grasping movements with either the LDH or the RNH.

VOI Definition

For each region included in the nine models the relevant time series was obtained from the fMRI data of each individual participant from the General Linear Model performed at the first level. The selection of VOIs was performed on both anatomical and functional bases: (i) for all participants, the average effect of the experimental manipulation (precision grip movements performed with LDH + precision grip movements performed with RNH; $p < 0.001$, uncorrected for multiple comparisons) was tested by means of a t-contrast, in order to detect brain activity underlying both movements; (ii) a Small Volume Correction (Worsley et al., 1996) was conducted on the resulting activation by considering the cytoarchitectonic probabilistic maps provided by the toolbox Anatomy (Eickhoff et al., 2007) as searching areas. The following maps were considered: AIP (Choi et al., 2006; Scheperjans et al., 2008), vPMC (Amunts et al., 1999), dPMC (Genon et al., 2016, 2018), and M1 (Geyer et al., 1996). Then, the first set of coordinates observed for each area (AIP left, AIP right, vPMC left, vPMC right, dPMC left, dPMC right, M1 left, and M1 right) was selected for the creation of the VOI. Concerning M1, the "hand knob" (Yousry et al., 1997) was adopted as the anatomical landmark to identify the set of coordinates for the creation of the VOI. For all participants, a spherical VOI of 5 mm radius was considered, built around the most significant set of coordinates detected through the SVC. This procedure was performed for each of the 8 regions included in the analysis. The time series extraction considered the "effects of interest" (t-contrast) adjusted for a F-contrast testing for the "effects of interest" and excluding any other regressor of no interest (motion parameters, errors, missed trials). The percentage of variance observed for each region was above 80% in all cases, and all VOIs included at least 10 voxels.

Model Estimation and Selection

Bayesian Inference (Penny et al., 2004) was performed to verify hypotheses concerning the "origin" of the hypothesized recruitment of ipsilateral regions during precision grip movements performed with the RNH and the LDH. We first verified whether and how (e.g., by means of LDH or RNH) the act of performing a precision grasping movement engages contra- and more importantly ipsilateral grasping regions. Bayesian Model Selection (BMS) was performed by means of random effects analysis (RFX; Stephan et al., 2009; Penny et al., 2010) accounting for the possibility that individual variance can be best described by different models. Model comparison was performed following a two-steps approach: (i) inference at a "family" level (i.e., subsets of models sharing specific peculiarities). In this study, two different families were built, on the basis of the origin of the modulation of inter-hemispheric connections (e.g., LDH-driven models; RNH-driven models). Then, (ii) Bayesian comparison was performed within the "winning" family, in order to reveal the model/s best fitting the data. Also the "null" model was included at this stage of the analysis, as to better explore dynamic causality hypotheses involving the two hemispheres.

RESULTS

GLM Group Analysis Results

A RFX analysis was conducted ($p < 0.05$, FWE-corrected for multiple comparisons, $k \geq 10$) as to verify the involvement of the considered brain regions (AIP, vPMC, dPMC, and M1) in our task. A t-contrast testing for selective effects of precision grip movements performed with the LDH or with the RNH was run within a mask involving the considered brain regions belonging to the grasping circuit. The contrast identified activation in all of these regions, in both hemispheres (see **Table 2** and **Figure 3**).

DCM Results

Effective connectivity patterns occurring among the considered brain regions were explored by means of DCM12, provided by the SPM12 toolbox (Wellcome Department of Imaging Neuroscience, London, UK), running in Matlab environment (R2017b, The MathWorks, Natick, MA, USA).

Family-Wise Results

BMS was adopted to evaluate which family model (LDH or RNH) better explained the data. The results indicated that the "LDH" family (e.g., movements performed with the LDH—models #1–4) was distinguished by the highest exceedance probability value (0.9732), while the "RNH" family (models #5–8) was consequently associated with a much lower value (0.0268—see **Figure 4A**). The winning family, LDH, is made up of 4 models sharing the hypothesis of inter-hemispheric connections between homologs areas (AIP, vPMC, dPMC, and M1) as driven by precision grasping executed with the LDH. These models assume this modulation as originating in the right hemisphere and spreading to the left hemisphere through one or more of the considered inter-hemispheric connections.

Model-Wise Results

As a second step, effective connectivity patterns were explored within the "LDH" family, in order to assess which model/s better fits the data. Results show (**Figure 4B**) that the "dPMC" model is associated with the highest exceedance probability (0.5671), followed by the "AIP" model (0.4113), the "M1" model (0.0123), the "vPMC" model (0.016), and the "null" model (0.0065). These results indicate that, among the considered models, those hypothesizing bidirectional inter-hemispheric modulations occurring either at the AIP (model #1) or at the dPMC (model #3) levels seem to better fit the data. The absence of modulation between hemispheres (model #9) appears to be the most unlikely hypothesis among the considered ones. In order to further characterize the results, parameter estimates of intra-hemispheric connections (DCM-A matrix) resulting from Bayesian Model Averaging (BMA) were extracted and tested against 0 (one-sample t-test, $p < 0.05$). This procedure was used to characterize both intra- and inter-hemispheric connection strengths between brain regions involved during the execution of PG movements with the RNH (left hemisphere) or the LDH (right hemisphere). The results are reported in **Table 3** and depicted in **Figure 5**. The statistical analysis showed that grasping with LDH and RNH significantly influences the selected input regions: the left AIP

TABLE 2 | Results of the RFX analysis ($p < 0.05$, FWE-corrected for multiple comparisons, $k \geq 10$).

CLUSTER level			PEAK level				MNI					
***p*(FWE)**	***k***	***p*(unc)**	***p*(FDR)**	***T***	**Z-score**	***p*(unc)**	***X***	***Y***	***Z***	**SIDE**	**REGION**	**BA**
<0.0001	**229**	**<0.0001**	**<0.0001**	**10.39**	**6.72**	**<0.0001**	**38**	**–16**	**65**	**RIGHT**	**PRECG**	**4**
			<0.0001	8.36	5.96	<0.0001	52	–10	35	**RIGHT**	PRECG	4
			<0.0001	6.66	5.18	<0.0001	35	–49	49	**RIGHT**	IPL	40
			<0.0001	6.65	5.12	<0.0001	42	6	59	**RIGHT**	MFG	6
<0.0001	**55**	**<0.0001**	**<0.0001**	**7.78**	**5.71**	**<0.0001**	**–38**	**–16**	**62**	**LEFT**	**PRECG**	**4**
			<0.0001	7.26	5.47	<0.0001	–31	–20	68	LEFT	MFG	6
			<0.0001	5.67	4.64	<0.0001	–28	–16	59	LEFT	MFG	6
<0.0001	**41**	**<0.0001**	**<0.0001**	**7.08**	**5.39**	**<0.0001**	**55**	**10**	**5**	**RIGHT**	**IFG**	**45**
0.030	**20**	**<0.0001**	**<0.0001**	**6.77**	**5.23**	**<0.0001**	**–51**	**7**	**15**	**LEFT**	**IFG**	**45**
0.016	**18**	**0.0001**	**<0.0001**	**6.50**	**5.10**	**<0.0001**	**–38**	**–30**	**38**	**LEFT**	**IPL**	**40**

The contrast of interest is precision grip_LDH + precision grip_RNH. PRECG, Precentral Gyrus; IPL, Inferior Parietal Lobule; MFG, Middle Frontal Gyrus; IFG, Inferior Frontal Gyrus. Bolded font indicates the first activation peak of the cluster (in terms of t and Z score).

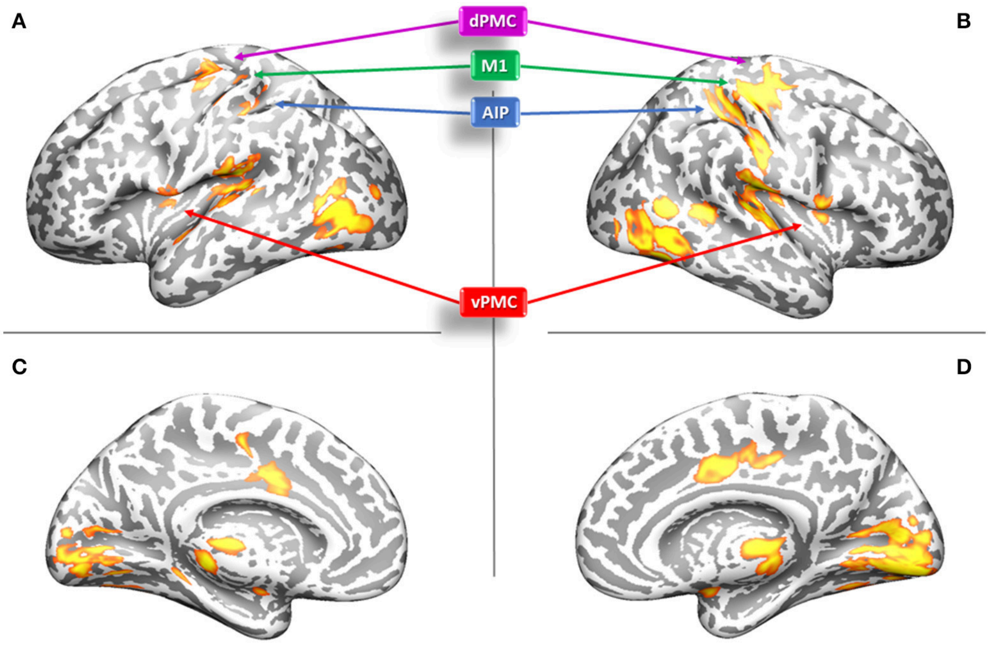

FIGURE 3 | Results of the group analysis (RFX) for the t-contrast RNH+LDH performed on the whole brain. **(A–C)** Left hemisphere, lateral and medial views; **(B–D)**: Right hemisphere, lateral and medial views. AIP, Anterior Intraparietal; vPMC, Ventral Premotor Cortex; dPMC, Dorsal Premotor Cortex; M1, Primary Motor Cortex.

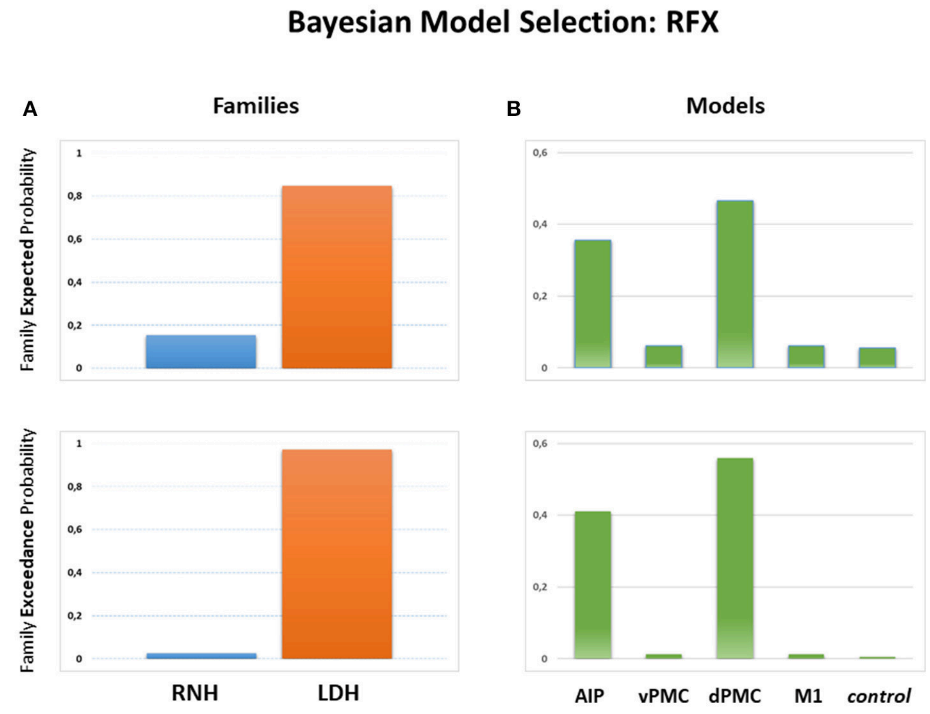

FIGURE 4 | Results of the BMS RFX performed at the family level **(A)** and at the model level **(B)** For both levels, expected (upper panels) and exceedance probabilities (lower panels) are indicated. LDH, Right Dominant Hand; RNH, Left Non-dominant Hand; AIP, Anterior Intraparietal; vPMC, Ventral Premotor Cortex; dPMC, Dorsal Premotor Cortex; M1, Primary Motor Cortex; Control, control model.

TABLE 3 | Results of one-sample *t*-tests performed on the parameter estimates related to input effects, intra-and inter-hemispheric connections within the winning family RNH ($p < 0.05$).

	INPUT	**AIP LEFT**	**AIP RIGHT**	**vPMC LEFT**	**vPMC RIGHT**	**dPMC LEFT**	**dPMC RIGHT**	**M1 LEFT**	**M1 RIGHT**
AIP LEFT	**$t_{(15)}$: 3.29** **$p = 0.0048$**		**$t_{(15)}$: 4.49** **$p = 0.0004$**						
AIP RIGHT	**$t_{(15)}$: 3.87** **$p = 0.0014$**	**$t_{(15)}$: −4.09** **$p = 0.0009$**							
vPMC LEFT		**$t_{(15)}$: 8.59** **$p < 0.0001$**			*$t_{(15)}$: −0.05* *p=0.9614*				
vPMC RIGHT			**$t_{(15)}$: 5.49** **$p < 0.0001$**	*$t_{(15)}$: 0.06* *p=0.949*					
dPMC LEFT				**$t_{(15)}$: 11.05** **$p < 0.0001$**			**$t_{(15)}$: 14.18** **$p < 0.0001$**		
dPMC RIGHT					**$t_{(15)}$: 10.91** **$p < 0.0001$**	**$t_{(15)}$: −2.69** **$p = 0.0164$**			
M1 LEFT						*$t_{(15)}$: 2.02* *p = 0.0.0612*			*$t_{(15)}$: 0.01* *p = 0.9982*
M1 RIGHT							**$t_{(15)}$: 4.42** **$p = 0.0004$**	*$t_{(15)}$: 0.01* *p = 0.9881*	

AIP, Anterior IntraParietal; vPMC, ventral PreMotor Cortex; dPMC, dorsal PreMotor Cortex; M1, Primary Motor Cortex. Cells on top of the columns report the "input" region and rows report the "target" region. Values in italic are not significant; values in bold are significant.

for precision grip movements performed with RNH $t_{(15)} = 3.29$ $p = 0.004$, and the right AIP for precision grip movements performed with the LDH, $t_{(15)} = 3.87$ $p = 0.001$. Concerning the left hemisphere, which is assumed to be primarily recruited when performing precision grip movements with the RNH (**Figure 5**), two out of three connections between nodes appeared to be significantly modulated [AIP-vPMC: $t_{(15)} = 8.59$, $p < 0.0001$; vPMC-dPMC: $t_{(15)} = 11.05$, $p < 0.0001$]. The connection dPMC-M1 showed a weak trend to significance [$t_{(15)} = 2.02$, $p = 0.06$]. Concerning the right hemisphere, primarily recruited in the control of precision grip movements performed with the LDH (**Figure 5**), all the connections appeared to be significantly modulated [namely AIP-vPMC: $t_{(15)} = 5.49$, $p < 0.0001$; vPMC-dPMC: $t_{(15)} = 10.91$, $p < 0.0001$; dPMC-M1: $t_{(15)} = 4.42$, $p = 0.0004$]. With regard to inter-hemispheric connections between homologous areas of the two hemispheres (**Table 3**, **Figure 5**), the functional link between AIPs appears to be significantly modulated in both directions [L→ R $t_{(15)} = 4.098$, $p = 0.0009$; R→ L $t_{(15)} = 4.492$, $p = 0.0004$]. While connections between vPMCs did not show any significant modulation effect in either directions, dPMCs connections appears to be significantly modulated in both directions [L→ R $t_{(15)} = 2.069$, $p = 0.0164$; R→ L $t_{(15)} = 14.18$, $p < 0.0001$]. Differently, connections between M1s did not highlight any significant result [L→ R $t_{(15)} = 0.01$, $p = 0.9981$; R→ L $t_{(15)} = 0.01$, $p = 0.9982$].

DISCUSSION

Despite their physical similarity, our two hands tend to play very different roles, with 90% of us showing the right hand dominance when using and interacting with objects, while the left hand has a merely supporting role. Only 10% of the population exhibits the reversed behavioral asymmetry, using the left hand as their dominant one. Thus, it is not surprising that the left-handers have been largely neglected in neuroimaging studies of human motor behavior, with most research focusing only on the right-handed population. To bridge this gap, we investigated the neural underpinnings of precision grasping movements in left-handed participants using a dynamic causal modeling approach (DCM; Friston et al., 2003).

In general, our results confirmed that performing a precision grasping task with either the left or the right hand recruits brain regions belonging to the grasping network, such as the AIP, the vPMC, the dPMC and the M1. We also explored whether and how the intra- and inter-hemispheric causal relationships between "key" cortical nodes of the parieto-frontal grasping network were influenced by the choice of the hand performing the movement in left-handers. For intra-hemispheric connectivity, we focused on the interactions between grasping region, as described by Castiello and Begliomini (2008), that are: AIP, vPMC, dPMC, and M1. For *inter-hemispheric* connectivity we considered two possible scenarios: (i) effective connectivity between homologous areas is affected by precision grasping movements performed with the RNH, given that this hand is supposed to play a "secondary" role with respect to the LDH; (ii) effective connectivity between hemispheres is modulated by the LDH, given the behavioral evidence that even in left-handers the left hand could be less skilled in tasks characterized by high levels of visuomotor processing, such as grasping small objects (Gonzalez et al., 2006, 2007). To test these hypotheses, left-handed participants performed precision grasping movements toward an object with either the right or the left hand.

In terms of the *intra-hemispheric* effective connectivity, we showed that when precision grip movements are performed with the RNH, the connections "AIP-vPMC" and "vPMC-dPMC" within the left hemisphere appear to be significantly modulated.

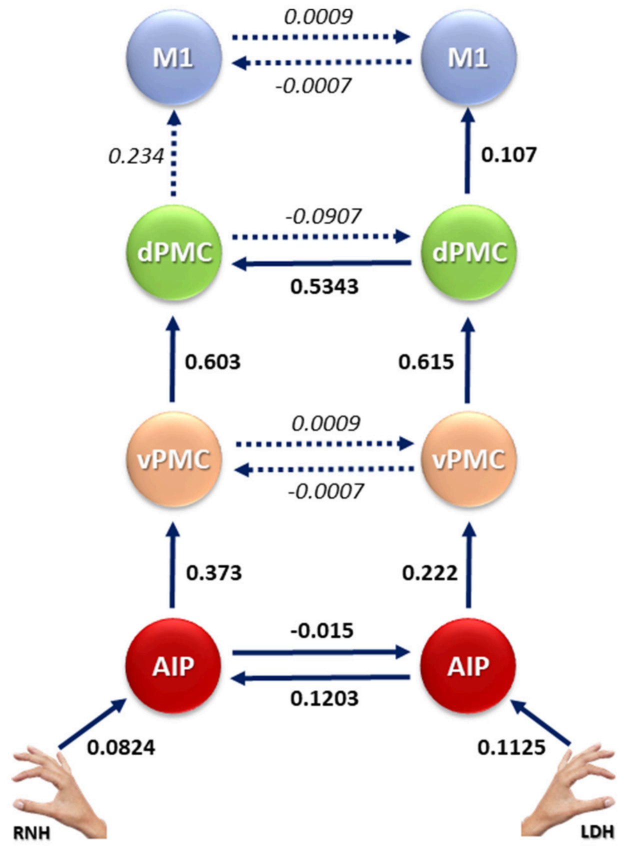

FIGURE 5 | Connection strengths of the tested models. Solid lines indicate significant modulation effects. Group-level averages of the MAP estimates and 95% confidence intervals are illustrated. The mean values were tested against 0. AIP, Anterior Intraparietal; vPMC, Ventral Premotor Cortex; dPMC, Dorsal Premotor Cortex; M1, Primary Motor Cortex.

On the other hand, when performing movements with the LDH, the "AIP-vPMC" and "vPMC-dPMC" connections within the right hemisphere were modulated. In addition, the "dPMC-M1" connection appeared to be modulated only within the right hemisphere, when using the LDH. No significant modulation effects were observed in the left hemisphere concerning the use of the RNH for the connection "dPMC-M1." These results are in line with recent studies showing that effective connectivity between intra-hemispheric nodes of the grasping network is specifically modulated by the choice of the performing hand (Begliomini et al., 2015). However, the fact that only within the right hemisphere (i.e., using the LDH) the final step of the circuit (dPMC-M1) appears to be significantly modulated by the performing hand might suggest that using the LDH requires a stronger "information flow" between these two areas as to accomplish the movement adequately. Overall, the pattern of connectivity observed within hemispheres confirms a series of results obtained in both humans and non-human primates (Rizzolatti and Luppino, 2001; Castiello, 2005; Castiello and Begliomini, 2008), converging on the idea that AIP and both ventral and dorsal regions of the premotor cortex act as "key" areas of the grasping circuit, together with the M1.

When considering *inter-hemispheric* connectivity, results showed that the best fitting models were those hypothesizing a RIGHT→ LEFT modulation when the LDH is used. These results speak in favor of a somewhat lower dexterity of the LDH as a modulating factor for inter-hemispheric connectivity between homologous areas. In other words, even if the left hand is supposed to be dominant for left-handers, it might be less skilled to properly accomplish a task requiring high levels of accuracy (i.e., precision grasping). Therefore, additional processing within the ipsilateral (left) hemisphere is required to support the right hemisphere.

Considering the stage at which this bilateral recruitment occurs, connectivity analyses indicated that the AIP and the dPMC are the key nodes for the inter-hemispheric "cross-talk": connections between the AIPs, as well as the dPMCs, appear to be significantly modulated in both directions. In both humans and non-human primates, the AIP plays a crucial role in "translating" object intrinsic properties into specific grips (Rizzolatti and Luppino, 2001). The present study confirms the bilateral involvement of the AIP in precision grasping tasks, previously observed in right-handers using either the right or the left hand (Tunik et al., 2005; Rice et al., 2006; Davare et al., 2007). For example, Davare et al. (2007) showed that hand shaping, the "core" event of a grasping movement, is impaired only when virtual lesions to both AIP are induced by means of repetitive transcranial magnetic stimulation (rTMS), while no impairment was observed when the AIP lesion was unilateral. The potential existence of a cross-talk between the two AIPs gives further support our present findings. Notably, previous DCM study on right-handers (Begliomini et al., 2015) observed only a LEFT→ RIGHT modulation during the execution of precision grasping movements performed with the left non-dominant hand. This result has been explained in terms of additional processing required by the right hemisphere, controlling the less-skilled left hand.

Considering right-handers, the dominance of the left hemisphere when using the right dominant hand in high precision tasks has been testified by many studies (Serrien and Sovijärvi-Spapé, 2015; Króliczak et al., 2016; see Corballis et al., 2012 for a review). The fact that left-handers were characterized by a bi-directional cross-talk when the LDH was used, confirms that the precision grasping task requires additional resources, not only as a result of the complexity of the task, but also because the performing left hand needs additional resources in terms of the visuomotor transformations, even if it is supposed to be the dominant and thus more the "efficient" one.

In a similar vein, the connection between the right and the left dPMC appeared to be modulated in both directions: this observation mirrors the results of a previous study involving right-handers (Begliomini et al., 2015). Other findings in right-handers also indicated that a precision grip performed with the left hand necessitates a contribution of the bilateral dPMC for an appropriate on-line monitoring of the action (Davare et al., 2006; Begliomini et al., 2008, 2015). This evidence provides support to the idea that dPMC plays a crucial role in controlling distal actions, which aligns with neurophysiological evidence showing the presence of neurons selective for the type of prehension in the dorsal premotor cortex of non-human primates (Area F2; Raos et al., 2003).

To summarize, the present study is the first to examine how connections among motor brain areas are affected by hand dominance in left-handers. The results speak in favor of a predisposition of the right hand/left hemisphere for motor tasks requiring high levels of dexterity, such as precision grasping. These results are consistent with those reported by previous behavioral observations (Gonzalez et al., 2006, 2007), suggesting that hemispheric specialization for visuomotor control might be handedness-independent. In this sense, right- and left-handers seem not to differ from each other: the right hemisphere involved in supporting the ongoing action recruits resources also from the left hemisphere to accomplish the action successfully. More precisely, performing a precision grasping task with the left hand highlights boosted inter-hemispheric connections between homologous areas (AIP and dPMC), suggesting the need of additional resources in terms of both visuomotor processing (AIP) and on-line monitoring (dPMC), both required to accomplish the action in an efficient manner. Additional studies on larger cohorts of left-handers (Mazoyer et al., 2016), and including populations characterized by different degrees of right- and left-handedness would be beneficial for a fine-grained exploration of the role of handedness in motor control.

In conclusion, the present study further validates neurophysiological and neuroimaging data on the cortical control of grasping in humans, adding novel insights on the intra- and inter-hemispheric interplay underlying grasping actions. Our results also contribute to fill the gap of knowledge on motor control in left-handers, shedding new light on the sophisticated interplay between handedness and motor control.

AUTHOR CONTRIBUTIONS

Experiment Conception: CB, LS, and UC; Experiment Data Collection: CB and LS; Experiment data analysis: CB, MD, and SB; Manuscript preparation: CB, LS, MD, SB and UC.

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What Are the Contributions of Handedness, Sighting Dominance, Hand Used to Bisect, and Visuospatial Line Processing to the Behavioral Line Bisection Bias?

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In a sample of 60 French participants, we examined whether the variability in the behavioral deviation measured during the classical "paper and pencil" line bisection task was explained by individual laterality factors such as handedness and eye sighting dominance, as well as the hand used to bisect, and the spatial position of the line to bisect. The results showed the expected main effects of line position and hand used to bisect, as well as some interactions between factors. Specifically, the effect of the hand used to bisect on the deviation bias was different as a function of handedness and line position. In right-handers, there was a strong difference between the biases elicited by each hand, producing a hand-used asymmetry, observed for each spatial position of the line. In left-handers, there was no difference in deviation as a function of hand used to perform the bisection, except when all factors triggered attention toward the left side such as bisecting left-displaced lines, with the left dominant hand, producing a strong leftward deviation as compared to the reduced bias exhibited with the right non-dominant hand. Finally, the eye sighting dominance interacted with handedness and line position. Left-handers with a right sighting dominance showed a leftward bias when they bisected left-displaced lines, while right-handers with a left sighting dominance showed an inversed bias when they bisected rightward lines. Taken together, these findings suggest that the behavioral deviation bias relies on the integration of the hemispheric weights of the visuospatial processing of the stimuli, and the motoric component of the hand used to bisect, as well as those linked to individual laterality factors. When all these factors producing asymmetric cerebral activation coincide in the same direction, then their joint effect will provide the strongest asymmetric behavioral biases.

Keywords: spatial attention, deviation bias, healthy participants, handedness, hand dominance, eye sighting dominance

INTRODUCTION

In neurologically intact individuals, much research has shown the existence of perceptual asymmetries during free-viewing conditions (for a review, Voyer et al., 2012). For example, during the "paper and pencil" line bisection task, usually used to assess hemispatial neglect (Heilman et al., 1985; Doricchi and Angelelli, 1999; Sperber and Karnath, 2016), non-clinical population exhibits a small but consistent tendency to slightly mark to the left of the veridical midpoint (Jewell and McCourt, 2000), referred to as pseudoneglect (Bowers and Heilman, 1980). This attentional orientation toward the left hemispace would be related to the asymmetrical control of spatial attention over the hemispheres (Mesulam, 1981; Kinsbourne, 1987; Driver and Vuilleumier, 2001; Corbetta and Shulman, 2011), with a stronger activation of the right hemisphere, being the dominant hemisphere for visuospatial attentional function (Kinsbourne, 1970; Mesulam, 1999), leading to an over-representation of the left side of space and a shift of the subjective center of the line toward that side. Recently, we demonstrated using fMRI during a line bisection judgment (LBJ) task that the degree of leftward behavioral bias was associated with the degree of rightward hemispheric lateralization (Zago et al., 2017).

Although this behavioral leftward bias is a reliable phenomenon (Jewell and McCourt, 2000), inter-individual variability exists both in the magnitude and the direction of the bias (Manning et al., 1990), and the demonstration of the factors that contribute to the variability of this bias remains open. For example, some studies have shown that visuospatial factors, such as the direction of the visual scanning of the line (Chokron and Imbert, 1993; Brodie and Pettigrew, 1996), the visual hemispace, and the hemispatial body field in which the line is presented (Bowers and Heilman, 1980; Luh, 1995; Mennemeier et al., 1997; McCourt, 1999) contribute to the behavioral attentional bias. When the visual scanning is initially performed from the left, it induced greater leftward deviations compared to right scanning (Brodie and Pettigrew, 1996; Chokron et al., 1998). In addition, lines positioned in the left hemispace induced more asymmetrical bisection than right-displaced lines (Luh, 1995; Mennemeier et al., 1997; McCourt, 1999). These visuospatial factors (visual scanning to the left and visual stimulation of left hemispace) would additionally activate the right hemisphere, and probably induce a stronger behavioral asymmetry.

In addition to these visuospatial components, the line bisection task also involves manual/motor components that are lateralized. Specifically, the hand used to perform the bisection and the handedness of the participants are two interacting (and sometimes confounding) factors that have been shown to modulate the bias (for a review, see Jewell and McCourt, 2000; McCourt et al., 2001; Hausmann et al., 2003). For example, the study of Luh (1995) reported a stronger leftward bias in left-handers than in right-handers (Luh, 1995), but both groups used their dominant (or preferred) hand to give the response, confounding the effects of handedness and hand used. The study of Scarisbrick et al. (1987) reported that left-handers using their left hand showed greater leftward bias during a visual line bisection task than right-handers using their left non-dominant hand (Scarisbrick et al., 1987). A greater leftward deviation bias was found in right-handers using their left non-dominant hand compared to their right preferred hand (Brodie and Pettigrew, 1996), while left-handers bisected horizontal lines toward the left when using the left dominant hand and more toward the right when using their right hand (Bradshaw et al., 1987; Dellatolas et al., 1996). Because each hand is controlled primarily by the contralateral hemisphere, the hand effect may reflect activation of the right-hemispheric sensorimotor areas for control of the left-hand, leading to higher global activation for the right hemisphere than the left hemisphere, which in turn leads to a larger leftward bias during bisection for left-hand use compared to right-hand use. In addition, as suggested by Brodie and Dunn (2005), moving the non-dominant hand (or non-preferred hand) during line bisection would require more conscious effort associated with extended and/or bilateral cortical activation that may modify the deviation bias (Brodie and Dunn, 2005).

Concerning the cortical organization of motor control, some studies tended to show differences between left- and right-handers. For example, Solodkin et al. (2001) reported that left-handers showed less brain lateralization than right-handers during a sequential movement task (Solodkin et al., 2001, but see Kroliczak et al., 2016). More recently, Tzourio-Mazoyer et al. (2015) demonstrated a different pattern of deactivation between left- and right-handers within the ipsilateral motor cortex during movement of the dominant hand (Tzourio-Mazoyer et al., 2015). Lastly, a rightward bias was found in left-handers using their preferred hand and when adopting a visual scanning from right to left (Brodie and Dunn, 2005), indicating an interaction between these factors. Taken together, these results suggest that the difference between left-handers and right-handers should be carefully investigated during line bisection task, and that the variability of the deviation bias would probably be explained by the interaction between manual/motoric and visuospatial factors.

Finally, eye sighting dominance, defined as the behavioral preference for one eye over the other under monocular viewing conditions (Coren and Kaplan, 1973; Porac and Coren, 1976; Coren, 1993) is an underscored individual laterality factor that could also contribute to the deviation bias during this visuomotor task. Although, it is known that each cerebral hemisphere processes information coming from the contralateral visual hemifield, recent imaging studies indicated that the ocular dominance is regulated by the ipsilateral occipital cortex. Specifically, the visual cortex ipsilateral to the dominant eye has been shown to be larger in size than the contralateral cortex (Erdogan et al., 2002), and the magnitude of the V1 response in the ipsilateral visual cortex of the dominant eye is greater during the stimulation of the dominant eye than that during the non-dominant one (Shima et al., 2010). Beyond the visual cortex, we observed using fMRI during a visually-guided saccade task that the rightward cerebral asymmetry of the dorsal frontoparietal attention network was more pronounced in left-handed participants with a right eye sighting dominance (i.e., eye/hand crossed) during basic shifts of attention in a visually guided saccade task (Petit et al., 2015). If the eye dominance induced stronger activation of the ipsilateral occipital cortex, this increased rightward cerebral lateralization could be the consequence of the functional connection between visual input and motor output within the right hemisphere for left-handers with a right sighting-eye (Petit et al., 2015). Finally, Chaumillon et al. (2014) demonstrated that this particular relationship between sighting dominance and ipsilateral cortex resulted in a shorter manual reaction times in response to lateralized visual target appearing in the contralateral visual hemifield with respect to the dominant eye (Chaumillon et al., 2014). Taken together, these findings highlight the need to consider eye dominance in studies investigating the processes underlying visuomotor actions, such as during line bisection.

The aim of the present study was to evaluate the effects of individual laterality factors such as handedness and eye sighting dominance, as well as of visuospatial and motoric factors related to the task to be performed, on the line bisection deviation bias. Specifically, in a sample of French participants enriched in left-handers, we examined whether the variability in the behavioral deviation measured during the classical "paper and pencil" line bisection task was explained by handedness, the hand used to bisect, eye sighting dominance, and the spatial position of the line to bisect. Based on the hypothesis that the amount of behavioral deviation bias obtained during line bisection would reflect the amount of cerebral activity elicited by the integration of different spatial attentional, motoric and visuospatial processes involved in the task, we predicted that the combination of these different factors would elicit stronger leftward deviation, such as in left-handers, who bisect left-displaced lines with their left dominant hand, perhaps with a right-eye sighting dominance. *A contrario*, we would expect to find a reduced leftward bias and even a rightward bias in right-handers who bisect right-displaced lines with their right dominant hand.

MATERIALS AND METHODS

Participants

We recruited 92 healthy volunteers, measured their hand preference and eye-sighting dominance (ESD), as well as the line deviation bias during a "paper and pencil" line bisection task. All participants provided written informed consent to participate in the experiment, and the protocol was approved by the ethics committee of Bordeaux University.

In the present study, due to the acknowledged difference in manual preference strength between right- and left-handers, we selected 60 participants with a strong (right or left) hand preference (see below). The mean age of this study sample was 22.9 years (*SD* = 3.5; range: 18–34 years).

Hand Preference

Hand preference was assessed using the Edinburgh inventory questionnaire (EI, Oldfield, 1971). Based on the distribution of EI scores obtained in a sample of 92 participants, we retained the upper (EI score $\geq$ to $+85$) and lower (EI score $\leq$ to -65) third of the population. Thus, the 29 selected left-handers (LH, 14 women) had a mean EI score of -81.2 (*SE* = 17.4), and the 31 right-handers (RH, 16 women) had a mean EI score of 97.8 (*SE* = 4.6). Note that there was a significant difference in the absolute EI value between the two groups $[t(58) = 5.1, p < 0.0001]$ due to both lower values and greater variability in the LH than in the RH. In addition, note that the sample of participants of this study is not representative of the general population, as it was deliberately enriched in left-handers.

Eye-Sighting Dominance

Eye-sighting dominance (ESD) was evaluated for each participant using a variation of the hole-in-the-card test (Durand and Gould, 1910). The participant was asked to extend his/her arms in front of him/her and to form a diamond-like frame using the thumb and index finger of both hands, replacing the card's hole to see through. He/she was then requested to stare through this frame at a specific object located at distance. Without moving his/her hands, the participant then had to look at the object using only one eye, first the right and then the left. The preferred sighting eye was determined to be that for which vision was the same as when looking with both eyes open. Note that using both hands to form a diamond-like frame avoids any bias due to a sighting measure using a single hand.

Among the 29 LH, 20 participants (including 9 women; mean age = 21.8 ± 3.2) showed a left eye-sighting dominance (L-ESD) and 9 (including 5 women; mean age = 23.4 ± 4.3) showed a right ESD (R-ESD). Among the 31 RH, 21 participants (including 11 women; mean age = 23.0 ± 3.2) had a R-ESD, and 10 (5 women; mean age = 24.7 ± 3.4) had a L-ESD.

Line Bisection Task: Procedure and Materials

The line bisection task contained 17 horizontal black lines of 1 mm width distributed on a white sheet of paper (landscape presentation), with a distance of 18 mm away from the left/right and upper/lower margins of the page. The lines that we used were similar to those used in the study of Hausmann et al. (2002). The lines ranged from 80 to 240 mm in length, in steps of 20 mm. They were pseudo-randomly positioned so that seven lines appeared in the middle of the sheet (one line of 100, 160, and 180 mm, two lines of 200 mm, and two of lines of 220 mm), and 10 lines were positioned either to the rightmost (five lines) or leftmost regions of the sheet (one line each of 80, 120, 140, 180 , and 240 mm). The sheet was laid in front of the participant's midline. Participants were instructed to bisect all lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. All participants bisected the lines from the top to the bottom of the page, and each line was covered after bisection. Participants completed the task twice, with their right and left hands. The order was counter-balanced across participants. There was no time restriction. The deviations to the left or to the right of the center were carefully measured to 0.5 mm accuracy. The percent deviation bias was computed using the following formula of Hausmann et al. (2002): [(measured left half – true half)/true half] × 100. The mean deviation bias was computed for each position of the lines (left, middle and right), separately for each hand used. Negative values indicate a left bias, whereas positive values indicate a bias toward the right.

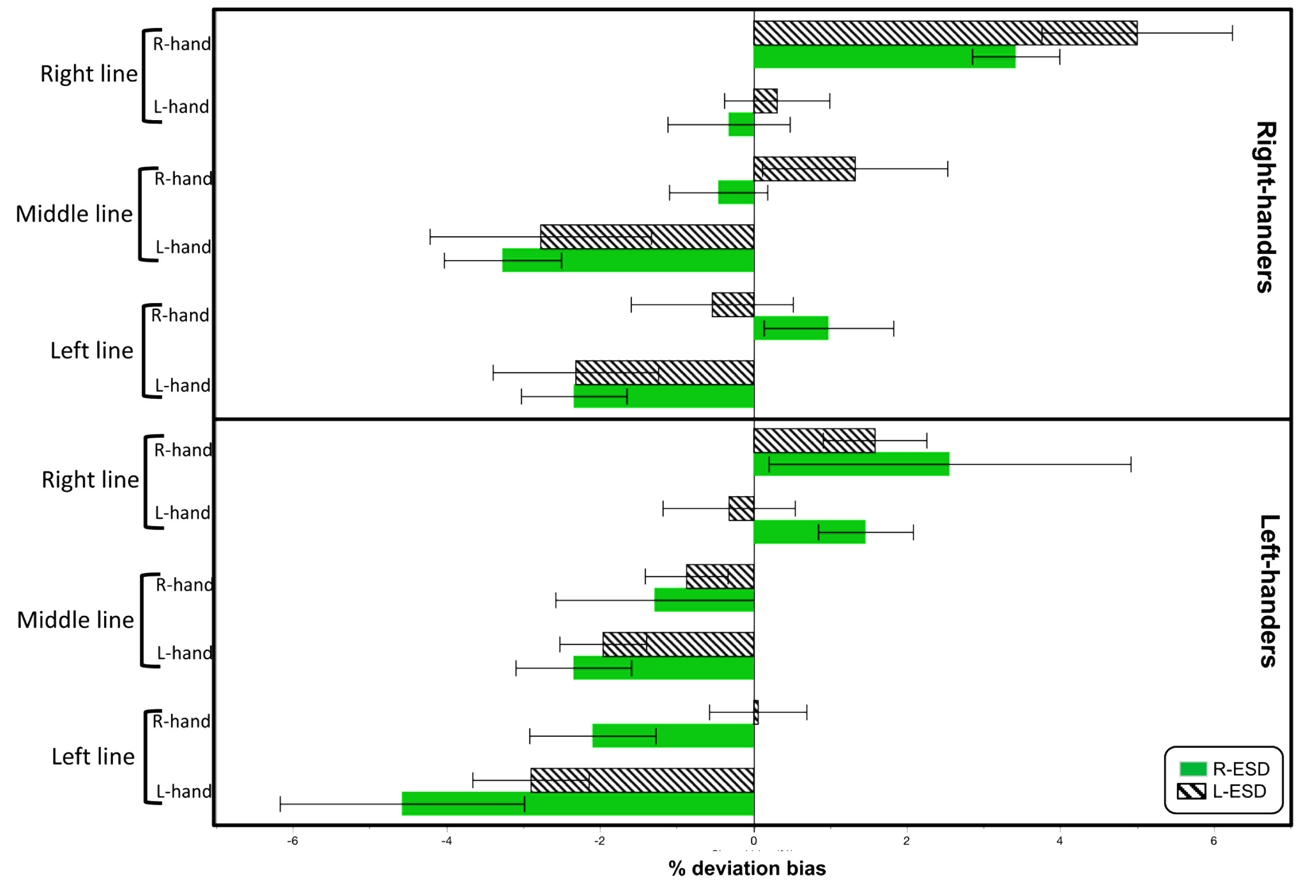

FIGURE 1 | Mean deviation bias (in %) during line bisection as function of Handedness, Eye sighting dominance (ESD), Hand used to bisect (L-hand and R-hand), and Line position (left, right, and middle).

Statistical Analyses

Statistical analyses were conducted using the ezANOVA function of the ez R-package (version 4.4-0)[1]. The deviation bias was analyzed with a mixed-model analysis of variance with repeated measures including "Eye sighting dominance" (ESD) and "Handedness" as between-subjects factors and "Hand used" (Left, Right) and "Line position" (left, middle, and right) as within-subjects factors. All *post hoc* comparisons were corrected for multiple comparisons using Bonferroni correction. Standardized effect size expressed in terms of generalized eta-squared (eta_G^2) value are reported (Bakeman, 2005). Effect sizes were characterized as small ($0.01 < \text{eta}_G^2 < 0.06$), medium ($0.06 < \text{eta}_G^2 < 0.14$) or large ($0.14 < \text{eta}_G^2$) according to published recommendations (Lakens, 2013).

RESULTS

Analysis of Deviation Bias

The distribution of mean deviation bias followed the Gaussian law (Shapiro-Wilk, $W = 0.9$, $p = 0.2$). On average, the deviation bias was −0.5 (± 2.2), indicating pseudoneglect [one-tailed *t*-test against zero, i.e., no bias; $t(59) = -1.7$, $p = 0.04$] over the sample of 60 participants. In terms of distance, the bisection mark was placed approximately 0.50 mm to the left of the true center (range in mm; −12.1; +11.4).

Descriptive statistics for each condition are shown in **Figure 1**. To test for the existence of pseudoneglect, we calculated Bonferroni-adjusted one-sample *t*-tests for each of the 24 different conditions (threshold of $p < 0.002$ Bonferroni-adjusted). Significant pseudoneglect was found in LH with L-ESD and in RH with a R-ESD when both groups bisected left-displaced and middle positioned lines with their left hand. Significant rightward deviation was found in RH with a R-ESD when they bisected right-displaced lines with the right hand.

Note that the largest values of leftward and right biases were found in LH with a R-ESD bisecting left-displaced lines with the left hand, and in RH with a L-ESD bisecting right-displaced lines with the right hand, respectively. However, these values did not reach the Bonferroni-adjusted threshold (LH R-ESD Left-hand left-line: $p = 0.02$, $n = 9$; RH L-ESD Right-hand right-line: $p = 0.003$, $n = 10$).

The ANOVA revealed two main effects. First, a "Line position" effect [$F_{(2,112)} = 36.3$, $p < 0.0001$; $\text{eta}_G^2 = 0.15$] showed

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[1] https://cran.r-project.org/web/packages/ez/index.html

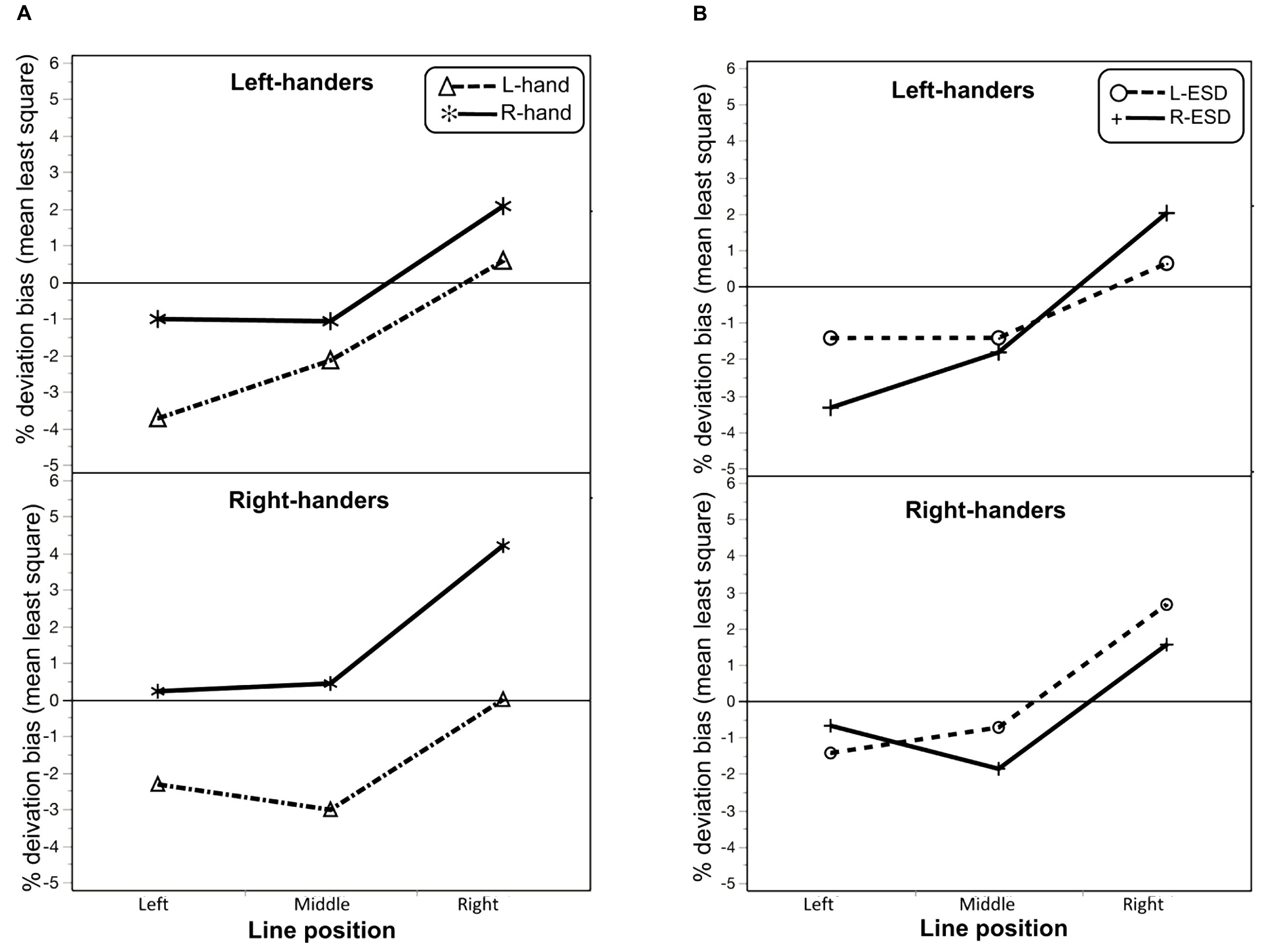

FIGURE 2 | (A) Interaction plot between the line position and the hand used to bisect (L-hand and R-hand) in left-handers and right-handers on deviation bias. **(B)** Interaction plot between the line position and Eye sighting dominance (L-ESD and R-ESD) in left-handers and right-handers on deviation bias.

that leftmost displaced lines (mean ± SD; −1.4 ± 2.9) and middle lines (−1.5 ± 2.5), both produced leftward deviation bias different from the rightward bias elicited by the rightmost displaced lines (+1.5 ± 3.1). Second, a "Hand used" effect [$F_{(1,56)} = 45.0$, $p < 0.0001$; eta$_G^2$ = 0.13] indicated that the left-hand elicited a leftward bias (−1.8 ± 2.6), while the right hand elicited an inversed bias (+0.8 ± 2.8).

In addition, the ANOVA revealed three interactions. One interaction was found between "Handedness" × "Hand used" [$F_{(1,56)} = 3.8$; $p = 0.05$; eta$_G^2$ = 0.01] and the other was found between "Handedness" × "Hand used" × "Line position" [$F_{(2,112)} = 5.4$; $p = 0.005$; eta$_G^2$ = 0.008]. As illustrated in **Figure 2A**, this last interaction indicated that a differential effect of the hand used to bisect between LH and RH on deviation bias as a function of line position. To further investigate this interaction, we computed *post hoc* comparisons Bonferonni-adjusted, revealing that, in LH, the difference between the left and right hand on deviation bias was significant for left-displaced lines only ($p = 0.01$), while for RH the difference between hands was significant for each line position (all p's < 0.0001).

A third interaction was found between "Handedness" × "ESD" × "Line position" [$F_{(2,112)} = 4.5$; $p = 0.01$; eta$_G^2$ = 0.02; **Figure 2B**], indicating a different effect of ESD between LH and RH as a function of line position. *Post hoc* comparisons Bonferonni-adjusted indicated that this difference between L-ESD and R-ESD was significant in RH when participants bisected middle lines ($p = 0.04$), with larger pseudoneglect for RH with a R-ESD. This difference was close to significance for right-displaced lines ($p = 0.06$), with RH with a L-ESD tended to show a larger rightward deviation that the one observed in RH with a R-ESD.

DISCUSSION

The aim of the present study was to evaluate the respective contributions of the visuospatial processing of the stimulus (here, the spatial position of the lines), the hand response (the hand used to bisect) as well as individual laterality factors such as the sighting dominance and the handedness to explain the variability of the behavioral attentional bias measured during the paper and pencil line bisection task.

First, the results demonstrated that, over the sample of participants, this free-viewing line bisection task produced a leftward deviation bias, congruent with the pseudoneglect well documented in the general population, as a result of right cerebral hemisphere dominance for spatial attention (Zago et al., 2017). As concerns the variability of this bias, the results of this study indicated a strong impact of both the spatial position of the stimulus and the hand used to bisect on the direction and magnitude of the deviation bias. In addition, these results also indicated that the variability of the deviation bias was also explained by interactions between individual laterality factors such as handedness and sighting dominance, and visuospatial and hand motoric variables related to the performance of the task.

These results replicate those of previous studies showing that the deviation bias is strongly affected by the position of the lines on the sheet as well as the hand used to perform the bisection (for a review, see Jewell and McCourt, 2000). More specifically, the results showed that both centered lines and left-displaced lines produced pseudoneglect, suggesting that these two positions triggered attention toward the left-side of space. By contrast, bisecting right-displaced lines reduced pseudoneglect, and produced an inversed bias. These findings are consistent with the behavioral results of a recent study measuring line bisection deviation in a large sample of more than 500 participants (Ocklenburg et al., 2018). Similarly, using the left hand induced greater leftward deviations than the right hand. Together, these findings demonstrated that the direction of the deviation bias is strongly triggered by the side of the visuospatial stimulation, as well as by the side of the motoric hand response, reinforcing the hypothesis of the visuospatial and motoric origins of pseudoneglect.

The interesting contribution of the present study is that the deviation bias was also modulated, although to a lesser extent, by individual laterality factors, indicating, as suggested by Learmonth et al. (2015), that the deviation bias is "a multicomponent phenomenon." As concerns handedness, the results demonstrated a different effect of hand used in function of line position between LH and RH. Specifically, in RH, each hand produced different deviation biases for each of the spatial position of the lines. By contrast, in LH, there was no difference in deviation bias between hands, except for left-displaced lines, for which the left dominant hand produced a strong leftward deviation that was significantly larger than the reduced bias exhibited with the non-dominant hand. Except for this specific condition, LH exhibited a lack of asymmetry between the hands that could be linked to the well-known lower behavioral hand-lateralization phenomenon observed in left-handers. Indeed, left-handers appear to have a lower difference in manual ability between their dominant and non-dominant hand due to a relatively preserved ability of their non-dominant hand, compared to the non-dominant hand of right-handers (Tzourio-Mazoyer et al., 2015). Even if we selected participants with a strong hand preference on the EI score, the group of left-handers still displayed a lower manual preference strength and larger variability than the group of right-handers. This lower manual asymmetry in LH was also expressed during this visuospatial/motor attentional task, during which the hand used factor has a lower impact than in RH. However, when all factors drive attention to the left (left dominant hand and left-displaced line), then the degree of pseudoneglect was maximized, suggesting a joint effect of these factors.

As concerns eye sighting dominance, the results indicated that this factor showed a subtle effect, evidenced in specific conditions, such as when individuals have a crossed hand-eye dominance. Specifically, the highest mean value of pseudoneglect was observed in LH with a right sighting dominance when they bisected left-displaced lines with the left-hand. In return, the highest value of inversed pseudoneglect was found in RH with a left sighting dominance when they bisected rightward lines with their dominant hand. Although additional studies are needed to confirm these observations by including a larger number of individuals with a crossed hand/eye dominance (Bourassa et al., 1996), these findings would suggest an additive combination of the hemispheric weights related to the different factors. If, as suggested by previous studies (Erdogan et al., 2002; Shima et al., 2010), eye dominance is predominantly controlled through the ipsilateral occipital cortex, then all factors of these two conditions would put activation weights on the same cerebral hemisphere, triggering attention contralateral to the most activated hemisphere.

Further neuroimaging investigations are now needed to understand the underlying cerebral mechanisms of this behavioral deviation bias. Based on our previous neuroimaging studies showing an association between the strength of the pseudoneglect and rightward cerebral asymmetries (Zago et al., 2016, 2017), and the evidence of right occipito-temporal regions underlying pseudoneglect measured with a perceptual line bisection judgment (Zago et al., 2017), we suggest that the specific condition that elicit the strongest behavioral pseudoneglect would also be associated with strongest rightward hemispheric asymmetries. It remains to further explore the respective cortical contributions related to hand and sighting dominance to explain inversed pseudoneglect.

CONCLUSION

The present work demonstrated that the variability of the behavioral bias measured during the line bisection task is explained by the integration of different factors related to the visuospatial processing of the stimuli and the motoric component of the hand used to bisect, as well as some individual laterality factors. When all these factors producing asymmetric cerebral activation coincide in the same direction, then their joint effect will provide the strongest asymmetric behavioral biases.

AUTHOR CONTRIBUTIONS

LZ designed the study, analyzed the data, and wrote the paper. AO performed the experiments.

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The Impact of Handedness, Sex, and Cognitive Abilities on Left–Right Discrimination: A Behavioral Study

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The present study examined the relationship between left–right discrimination (LRD) performance and handedness, sex and cognitive abilities. In total, 31 men and 35 women – with a balanced ratio of left-and right-handers – completed the Bergen Left–Right Discrimination Test. We found an advantage of left-handers in both identifying left hands and in verifying "left" propositions. A sex effect was also found, as women had an overall higher error rate than men, and increasing difficulty impacted their reaction time more than it did for men. Moreover, sex interacted with handedness and manual preference strength. A negative correlation of LRD reaction time with visuo-spatial and verbal long-term memory was found independently of sex, providing new insights into the relationship between cognitive skills and performance on LRD.

Keywords: left–right discrimination, handedness, sex difference, cognitive abilities, visuo-spatial, language

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INTRODUCTION

The ability to discriminate left from right, called left–right discrimination (LRD), is essential in everyday life. Whether the task is following directions to an unknown place or operating on a patient's knee, it is necessary to be able to differentiate left from right. It is reasonable to assume that such an essential ability would be mastered by most people. However, many people report difficulties discriminating left from right in daily life (Hannay et al., 1990), resulting in what we call Left–Right Confusion. Moreover, very few healthy people have trouble discriminating up from down (Hirnstein et al., 2009). The lack of difficulty in up–down discrimination may be due to the strong up–down asymmetry of our world, induced by gravity (Vingerhoets and Sarrechia, 2009). Hence, this spatial confusion phenomenon seems specific to left–right discrimination. LRD can be divided into two types: egocentric and allocentric (Auer et al., 2008). Egocentric LRD is the ability to discriminate left from right from one's own perspective with typical orientations. Allocentric LRD is used for unusual orientations or for other people's bodies and is said to be an association of egocentric LRD with mental rotation. The present work used the Bergen Left–Right Discrimination Test (BLRDT, Ofte and Hugdahl, 2002a,b), which focuses on allocentric LRD.

Left–right discrimination can be assessed through different measures. Older studies (e.g., Hannay et al., 1990) often used self-report questionnaires exclusively (questionnaires on subjective LRD performance in daily life). Most recent studies have used behavioral tasks such as BLRDT instead of self-report, or coupled self-report questionnaires with behavioral tasks (e.g., Jordan et al., 2006). Those studies identified several factors explaining LRD variability, including sex, handedness and education.

Sex differences in self-reported left–right confusion are found repeatedly. According to the results of questionnaires, women are more prone to left–right confusion compared with men (Hannay et al., 1990; Jordan et al., 2006; Gormley et al., 2008; Hirnstein et al., 2009; Hirnstein, 2011; Ocklenburg et al., 2011; Slagman, 2014; McKinley et al., 2015). However, performance reported by women is inconsistently correlated to their performance of actual behavioral tasks, with some studies reporting moderate correlation between the two (Gormley et al., 2008; Vingerhoets and Sarrechia, 2009; Thomas et al., 2013; Grewe et al., 2014; McKinley et al., 2015) and others reporting no correlation (Jordan et al., 2006; Hirnstein et al., 2009). Compliance with sex stereotypes may be the reason for women's lower scores on self-reports (Jordan et al., 2006). Some studies also find sex differences when behavioral tasks are analyzed (Ofte, 2002; Ofte and Hugdahl, 2002a; Gormley et al., 2008; Hirnstein et al., 2009; Ocklenburg et al., 2011; Hjelmervik et al., 2015; McKinley et al., 2015) but other studies do not find such differences (Hirnstein, 2011; Hirnstein et al., 2011; Thomas et al., 2013; Grewe et al., 2014). Finally, one study reported sex differences in behavioral tasks only in participants from 18 to 22 years old. In studies with a wider age range, a sex difference has either not been found or not been reported in older adults (Ofte and Hugdahl, 2002a). Thus, the effect of sex on left–right discrimination remains an open issue, with one possible explanation being that sex interacts with other factors such as handedness. The sample of participants in the present study was balanced for sex and handedness, thus maximizing the possibility that evidence for such an interaction could be found.

Another factor affecting LRD may be handedness. Indeed, Hannay et al. (1990) found that right-handers reported fewer difficulties than left-handers in LRD. Moreover, Ofte (2002) found that left-handed men performed better than right-handed men on the BLRDT. Yet, there are many studies that do not report a significant difference between left-handers and right-handers (Jaspers-Fayer and Peters, 2005; Jordan et al., 2006; Gormley et al., 2008; Vingerhoets and Sarrechia, 2009; Grewe et al., 2014; Slagman, 2014; McKinley et al., 2015). It should be noted, however, that there are no studies with a ratio of left-handers above 15%. Moreover, most studies are based solely on self-reports, which have proven to be unreliable (Jordan et al., 2006). In addition, Vingerhoets and Sarrechia (2009) demonstrated that handedness had no impact on its own but that stronger manual preference strength and asymmetry were correlated with better performance. We aimed to investigate more thoroughly the debated difference in LRD between left-handers and right-handers by including a high ratio of left-handers (41%) and taking into account the strength of handedness. We also investigated sex difference and its potential interaction with handedness. Additionally, Marzoli et al. (2015) demonstrated that in a task with pictures of ambiguous human silhouettes performing one-handed manual action, both left- and right-handers were more prone to say that the silhouettes were performing the action with the right hand. The authors hypothesized that both left- and right-handers had "an attentional bias toward the right-arm." Therefore, unlike previous LRD studies, we aimed to determine whether such a bias could be found in LRD.

Finally, the cognitive abilities factor was explored. Ofte and Hugdahl (2002a) found that children younger than 8 years old exhibit the lowest LRD performance (12%). Adolescents (12–13 years old) and older adults ($M = 67$) had better performance (40%). Young adults (18–22) had significantly better performance than all groups (60%). This finding supports the assumption that LRD is a developmental skill (Piaget, 1929; Elkind, 1961). Moreover, LRD performance seems to follow the same declining trend as spatial cognitive abilities in older adults (Techentin et al., 2014). Benton (1968) proposed that one component of LRD is visuo-spatial ability. Accordingly, students' academic curriculum has been found to influence their left–right discrimination performance, with medical students performing better than law and psychology students (Ofte, 2002). The fact that medical students are more proficient at LRD and have stronger spatial abilities strengthens the potential relation between LRD and spatial cognitive performance. In addition, medical students who wanted to be surgeons had better LRD scores than those wanting to be general practitioners or medical doctors (Gormley et al., 2008). It was hypothesized that this enhancement may be due to the more frequent use of spatial abilities among future surgeons than among other medical students. Note, however, that the nature of the visuo-spatial skills related to strong performance in LRD remains to be defined, as previous studies failed to demonstrate a relationship between LRD and scores on a Mental Rotations Test or between LRD and a navigation task in a 3D virtual maze (Jordan et al., 2006; Ocklenburg et al., 2011). In addition, Benton suggested that LRD entailed a verbal component, including the attribution of words to the concept of left and right. However, the relationship between verbal ability and LRD performance has been poorly investigated in adults.

Consequently, we investigated the relation of visuo-spatial cognitive abilities and LRD using more tests and extended this assessment to verbal cognitive abilities, the underlying hypothesis being that the participants with more developed abilities would either have shorter reaction times or make fewer errors.

Unlike most studies, which use behavioral tasks to assess proficiency in LRD, we focused not only on the error rate but also on the reaction time. Previous studies using the BLRDT used a pen-and-paper version, with limited time to complete a maximum number of items. We used a computerized version with one stimulus at a time and no total time limit. Our assumption was that LRD performance could be measured by both accuracy and processing time.

In summary, this work intended to unravel the relationships between sex, handedness and abilities in language, verbal memory and visuo-spatial domains in left–right discrimination. So far, the effect of these factors has been studied apart. It has previously been shown that interactions between these factors could affect cognitive performances (Mellet et al., 2014a). The present work investigated whether such interactions could also affect performances in left–right discrimination, which could explain the lack of consensus regarding their role in the inter-individual variability of LRD. In addition, the parameters of the task which modulated its difficulty such as the number of arms crossings or the orientation were included in the analysis.

MATERIALS AND METHODS

Participants

The study was approved by the Basse-Normandie local Ethics Committee CPP Nord-Ouest III. 66 participants (31 men, 35 women) were included in this study and underwent the BLRDT. Extensive cognitive testing was available in 55 participants who belonged to the BIL&GIN database (Mazoyer et al., 2016). The mean age was 24.5 ± 4.5 years for women and 25.5 ± 7 years for men. The mean level of education (years since first grade) was 16.1 ± 2 years for women and 15.8 ± 2.2 years for men.

Procedure and Tests

Handedness

The participants were asked to self-report their handedness. According to the responses, there were 27 left-handers (41%, 14 women, 13 men) and 39 right-handers (59%, 21 women, 18 men), which is well above the typical population ratio for left-handers (∼10%; Annett, 1970; Hécaen, 1984).

Handedness was further assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The test comprises 10 items assessing the preferred hand of the participant in daily use and in the manipulation of various objects and tools. The BIL&GIN version of the Edinburgh Handedness Inventory was used with the "broom" item excluded since very few young people had enough familiarity with this tool. A score of −100 indicates strong left-handedness whereas a score of +100 indicates strong right-handedness.

The left-handers' score ranged from −100 to +17.6, with a mean of −58.6 ± 39.8. For right-handers, the range was +25 to +100 with a mean of +90.3 ± 18.1. The fully lateralized (−100 or +100) represented 64.1% (25 participants) of the right-handers and 33.3% (9 participants) of the left-handers. Such a difference is consistent with other studies (Mellet et al., 2014a); a common explanation is the fact that left-handers are under-represented in the general population (∼10%; Annett, 1970; Hécaen, 1984) and have to adapt to a right-handers' world. Finally, 18 women were not fully lateralized and 17 were fully lateralized.

Assessment of Cognitive Skills

Fifty-five among 66 participants performed a series of 10 cognitive tests.

Four tests assessed their spatial cognition. The first test was the Mental Rotation Test (Vandenberg and Kuse, 1978), which assesses performance in mental rotation. The second was the Raven Progressive Matrices (Raven, 1956) test, which assesses non-verbal reasoning. The third was the Corsi block-tapping test (Della Sala et al., 1999), which assesses visuo-spatial working memory.

The fourth test was an in-house virtual maze test that assesses topographic memory. The participants first had to memorize a survey perspective 2D map of the maze, which contained seven items. They then switched to a 3D route perspective of the maze, and the examiner asked them to retrieve items in a specific order. When they retrieved an item, they were given the name of the next item to retrieve. The score is dependent on the number of items retrieved and the time spent to retrieve each item.

Two tests assessed verbal long-term memory. First, the participants performed a custom version of Rey's 15 words list (Rey, 1958). The custom version had 18 words in order to palliate a ceiling effect observed during the non-delayed recalls. The participants listened to the list five times. At the end of each listening session, they had to recall as many words as they could. Twenty minutes later (with no verbal tasks in between), they had to recall as many words as possible from the list. The collected variable was the number of words retrieved after the 20-min lapse.

Secondly, the participants performed the same task with a list of 15 pseudo-words. The variable considered was the number of pseudo-words retrieved after the 20-min lapse.

Verbal working memory was assessed through two tasks. The first was the Reading Span Test (Daneman and Carpenter, 1980; Desmette et al., 1995), and the second was the Listening Span Test (Daneman and Carpenter, 1980).

In the Reading Span Test, the participants read sentences on a computer screen. The number of sentences increased after each block (first 3 × 2 sentences, then 3 × 3 and up to 3 × 6). The participants had to read each sentence out loud and, at the end of a block, they had to recall the last word of each sentence.

The Listening Span Test followed the same pattern, except that each sentence was read by the examiner and, instead of reading it out loud, the participant had to determine whether it was in the present tense.

The participants completed a vocabulary test (Binois and Pichot, 1956) where they had to find, in a list of 6 words, the synonym of a given word. There were a total of 46 given words.

The participants also performed a verb generation task. They heard a pre-recorded list of words, with 10 s between each word. During this lapse of time, they had to list as many verbs as they could, related to the word they heard.

Bergen Left–Right Discrimination Test

A computerized version of the pen-and-paper concrete version (Ofte and Hugdahl, 2002b) of the BLRDT (**Figure 1**) was used. Stimuli were presented electronically on a laptop using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, United States).

The stimulus set was composed of 96 line drawings of a figure; 50% of the figures were presented from the back and 50% from

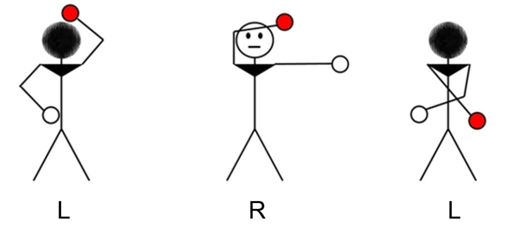

FIGURE 1 | The Bergen Left–Right Discrimination Test. Participants had to decide by button press whether the labels 'R' or 'L' below the figure matched the left or right hand highlighted in red. In this example, the first item is incorrect while the second and third items are correct.

the front. When the head of the figure was black, it meant it was viewed from the back. When a face was drawn, it meant the figure was viewed from the front. The arms of the figure had different positions, with no, one or both arms crossing the central line of the body. The presentations of each crossing condition were balanced. The target hand (colored in red) was the left-hand half of the time, and it was the right-hand the other half of the time. Under the figures were the letters "D" or "G" (French abbreviation for Right or Left), and the participants had to determine whether the letter was congruent with the target hand. Due to a labeling error, the congruent situation was presented 47 times, and the incongruent was presented 49 times.

To answer, the participants had to press either 8 (congruent) or 5 (incongruent) on a numpad. The keys were labeled with a green sticker marked "Vrai" (True) on 8 and a red sticker marked "Faux" (False) on 5. The keys were arranged vertically to prevent a stimulus-response effect.

Stimuli were presented in a randomized order; the participants had no time restrictions and were simply instructed to answer as soon as they felt they had the correct answer. After each response, a blank screen was presented for 1000 ms before the next stimulus appeared.

The analyses entailed computing reaction times for correct answers and for error rates.

Statistical Analysis

Statistical analysis was conducted with the JMP software (SAS, Cary, United States, version 13.2).

A total of 96 measures per participant were collected. The outliers in reaction time were excluded from the analyses using Tukey's method, excluding values below the 1st quartile − 1.5 × Inter Quartile Range and above the 3rd quartile + 1.5 × IQR. In total, 388 (6.1%) values above 5348 ms were excluded, and 32 were wrong answers. To perform reaction time analyses, we excluded the remaining 194 wrong answers, resulting in a total of 582 (9.2%) values being excluded.

A repeated-measures 3 (Crossings) × 2 (Orientation) × 2 (Target hand) × 2 (Sex) × 2 (Handedness) × 2 (Manual Preference Strength) ANOVA on reaction times was performed. The within-participants factors were Crossings (0, 1, or 2 arms crossing the midline of the stickman), Orientation (Front or Back view) and Target hand (Right or Left). The between-participants factors were Sex, Handedness and Manual Preference Strength (MPS). MPS was set to MPS+ for participants with either −100 or +100 Edinburgh scores, and it was set to MPS- for the others.

The effect of between-subject factors on error rate was assessed with a 2 (Handedness) × 2 (MPS) × 2 (Sex) ANOVA. An outlier participant was excluded.

A 2 (Label) × 2 (Target hand) × 2 (Handedness) × 2 (Sex) repeated-measures ANOVA on reaction time was performed to determine whether the label or congruency (corresponding Label and Target hand) had an effect and whether such an effect would be influenced by Handedness or Sex.

A Principal Components Analysis (Promax rotation) was performed to reduce the resulting matrix of standardized scores from the ten verbal and visuo-spatial tests. The scree criterion was used to determine the number of factors to include. This resulted in a four-component solution that explained 60.9% of the variance.

The first was a Spatial Cognition component that aggregated the Raven matrices, the Mental Rotation Test, the maze test and the Corsi block test and explained 20.1% of the variance (loading factors: 0.92, 0.63, 0.57, 0.43, respectively). The second was a Verbal Long-term Memory component that aggregated Rey's 18 words test and the pseudo-words test and explained 14.3% of the variance (loading factors: 0.88, 0.75, respectively). The third was a Verbal Working Memory component that aggregated the Reading Span Test and the Listening Span Test, explaining 13.3% of the variance (loading factors: 0.98, 0.42, respectively). The last was a Lexical component that aggregated the vocabulary test and the verb generation test and explained 13.3% of the variance (loading factors: 0.98, 0.32, respectively).

A multiple linear regression was computed to assess the relationship between the reaction time and the four components evidenced by the PCA. The same analysis was also conducted on the mean error rate. In the original sample of the BIL&GIN (436 adults), no differences were found between left- and right-handers on any of the cognitive components, and a significant difference was found – in favor of men – on the spatial cognition component (Mellet et al., 2014a). In our subsample, there was a significant difference in favor of men in the spatial cognition (p = 0.0010) and in the verbal working memory (p = 0.0393) components. There was a significant difference in favor of women in the verbal long-term memory (p = 0.0032) component, while Handedness had no significant impact on any of the components. Therefore, Sex was included as covariate in the linear regression.

RESULTS

Effects of Sex, Handedness, and Manual Preference Strength

A significant main effect of the number of Crossings was found, $F(2,111) = 106.04$, $p < 0.0001$, $\eta_p^2 = 0.66$. Tukey's *HSD* showed that all levels were significantly different (all $ps < 0.0001$) with no crossing being the easiest, one crossing being intermediate and two crossings being the hardest. There was a significant interaction between number of Crossings and Sex, [$F(2,111) = 3.09$, $p = 0.0493$, $\eta_p^2 = 0.05$, **Figure 2**, left]. Although, no *post hoc* tests survived to the Tukeys's correction, this interaction indicated that women's reaction times tended to be more affected by the increasing number of crossings (i.e., the task difficulty) compared with the reaction times of men.

The ANOVA revealed a significant main effect of Orientation, $F(1,57) = 4.94$, $p = 0.0301$, $\eta_p^2 = 0.08$. Participants were faster to respond on back-view stimuli ($M = 2374 \pm 76$ ms) than front-view stimuli ($M = 2462 \pm 76$ ms).

No main effect of Sex ($p = 0.3755$) or Handedness ($p = 0.1155$) was found on reaction time, but interactions with intra- or between-subjects factors were evidenced (see below). A main effect of sex was evidenced on error rate: $F(1,57) = 5.24$, $p = 0.03$, $\eta_p^2 = 0.08$ (**Figure 2**, right). Women had a higher error rate ($M = 4 \pm 0.4\%$) than men ($M = 2.6 \pm 0.4\%$).

The interaction for Handedness and Target hand was significant on reaction time, $F(1,54) = 16.00$, $p = 0.0002$, $\eta_p^2 = 0.23$ (**Figure 3**, left). Tukey's *HSD* showed that the left-handers were significantly ($p = 0.0012$) faster when the left hand ($M = 2203 \pm 116$ ms) rather than the right hand ($M = 2399 \pm 116$ ms) was the target. Correspondingly, the error rate was lower for left hands than for right hands in left-handers (2.5% and 4.6%, respectively, $p = 0.02$ paired t-test). No difference was found for right-handers ($p = 0.45$).

A marginally significant interaction for Sex and MPS was found, $F(1,58) = 3.71$, $p = 0.06$, $\eta_p^2 = 0.06$. Women MPS- tended to be slower than men MPS-. The interaction was more complex concerning the error rate, involving Sex, MPS and Handedness [$F(1,57) = 7.75$, $p = 0.007$, $\eta_p^2 = 0.12$]. Women MPS- made more errors than men MPS-, but this result was found among right-handers only [*Post hoc* t-test: $t(11)$, $p = 0.02$].

A significant interaction between Label and Handedness (**Figure 3**, right) was revealed, $F(1,60) = 13.09$, $p = 0.0006$, $\eta_p^2 = 0.18$. A *post hoc* Tukey's *HSD* showed that left-handers were significantly faster ($p = 0.0104$) when the label "L" ($M = 2256 \pm 109$ ms) was presented rather than the label "R" ($M = 2374 \pm 109$ ms). Such an advantage was also found in the error rates, which were lower for the label "L" than for the label "R" in left-handers (2.5 and 4.6%, respectively, $p = 0.03$, Wilcoxon). No difference could be found for right-handers ($p = 0.29$).

A significant interaction between Label and Target hand was also found, $F(1,60) = 116.43$, $p < 0.0001$, $\eta_p^2 = 0.66$. *Post hoc*

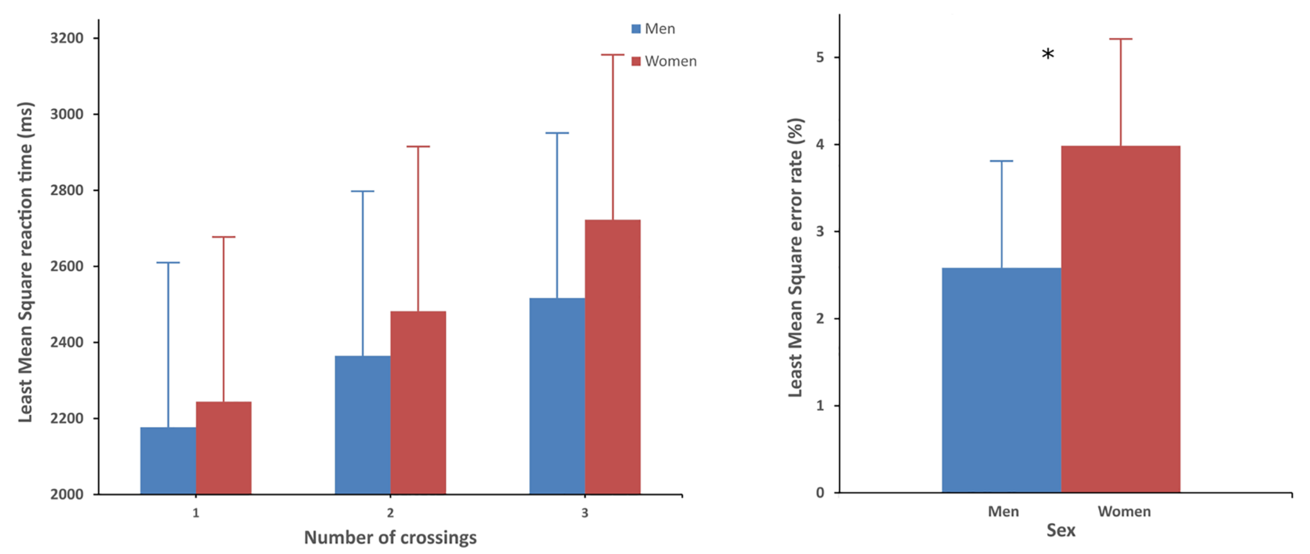

FIGURE 2 | Left: Interaction between Sex and the number of Crossings on reaction time. **Right**: Error rates for women and men. Error bars represent inter-group Confidence Interval (95%). *Represents significant difference ($p < 0.05$).

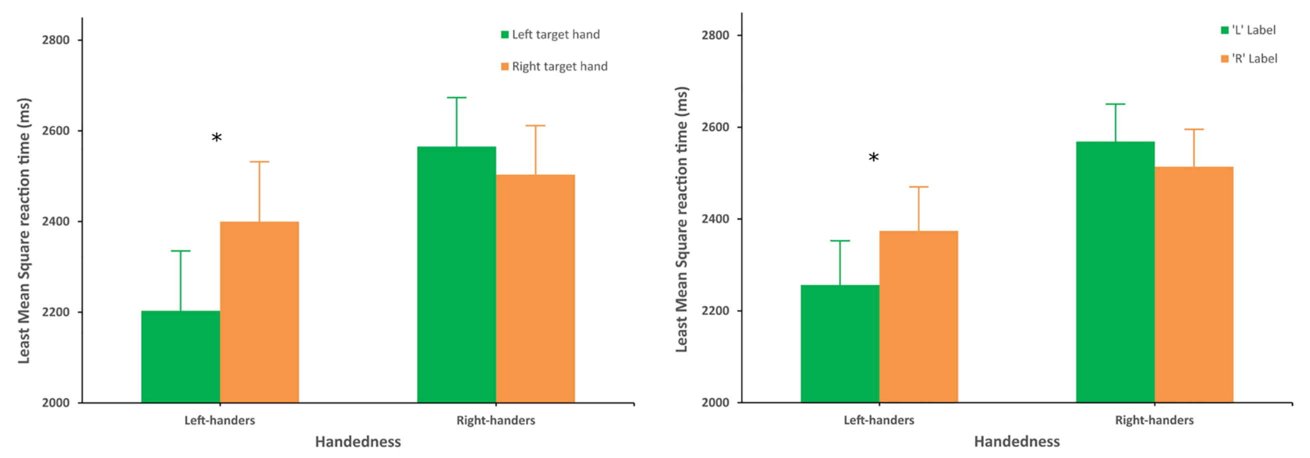

FIGURE 3 | Left: Interaction between Handedness and Target hand on reaction time. Left-handers were significantly faster when the left hand rather than the right hand was the target. *Represents significant difference ($p < 0.05$). **Right**: Interaction between Handedness and Label on reaction time. Left-handers were significantly faster when the label "L" was presented. Error bars represent intra-group Confidence Interval (95%). *Represents significant difference ($p < 0.05$).

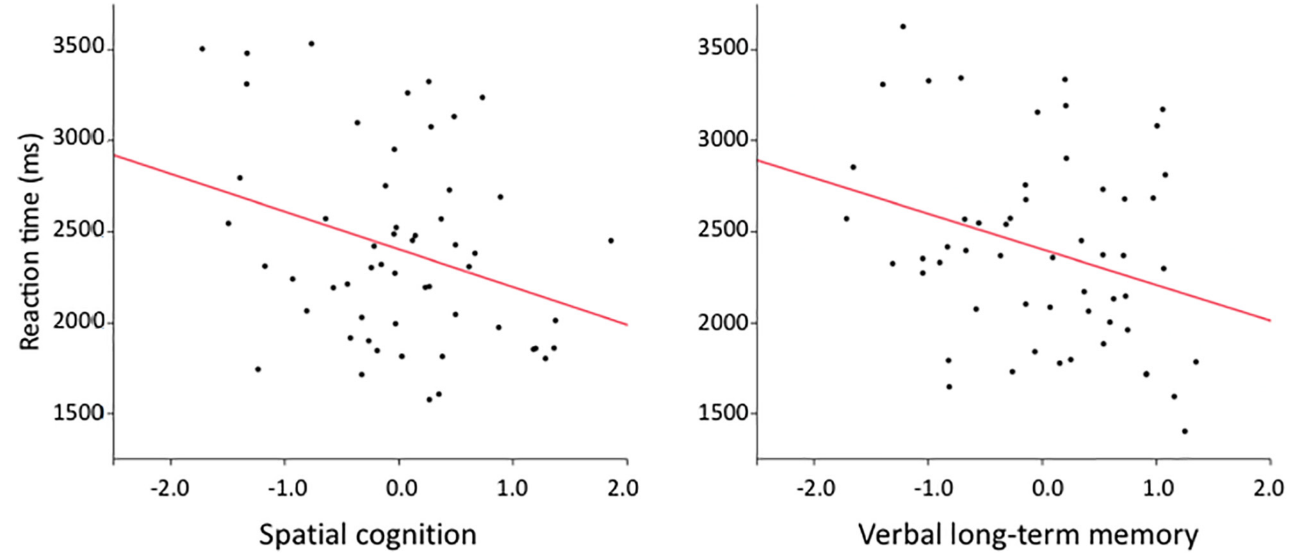

FIGURE 4 | Negative correlation between the reaction times and the normalized score on the spatial cognition component **(left)** and the verbal long-term memory component **(right)**.

Tukey's *HSD* showed that participants were significantly faster (∼267 ms) when the label was congruent with the target hand ($p < 0.0001$). No such difference was found for error rate ($p = 0.34$, Wilcoxon).

Correlation of LRD Performance With Cognitive Abilities

A significant correlation was found between reaction times on the BLRDT and cognitive abilities, $F(5,49) = 3.4282$, $p = 0.0098$, $R^2 = 0.26$. *Post hoc* analysis revealed that reaction times to the BLRDT were negatively related to the Spatial cognition score, $t(49) = -2.27$, $p = 0.0278$, and the Verbal Long-term Memory score, $t(49) = -2.20$, $p = 0.0326$ (**Figure 4**). Participants' mean reaction time was 2404 ms and decreased by 207 ms for each point in the spatial cognition component and by 196 ms for each point in the Verbal Long-term Memory component.

No significant correlation was found between cognitive abilities and the error rate, $F(5,48) = 0.71$, $p = 0.40$, $R^2 = 0.07$.

Summary of the Results

The reaction time increased significantly with the number of crossings. It also increased significantly for the front-view over the back-view.

Women had longer reaction times than men as the number of crossings increased, and they made significantly more errors than men. Not fully lateralized right-handed women made significantly more errors than not fully lateralized right-handed men.

Left-handers were significantly faster at identifying left target-hands over right target-hands, and they were significantly faster when the label "L" was presented over the label "R". They also made significantly fewer errors on the left target-hands over the right target-hands. Both left- and right-handers exhibited a congruency effect: reaction time was significantly shorter when the label matched the target hand.

Finally, reaction times were negatively correlated with the Spatial Cognition and the Verbal Long-term Memory components of the PCA.

DISCUSSION

The main aim of the present study was to investigate the variability in behavioral performance differences in LRD using the Bergen Left–Right Discrimination Test (BLRDT). Unlike most of the previous studies, we focused not only on the error rate but also on the reaction time as indicators of performance. We aimed to determine whether handedness was a significant factor of variability in LRD performance by analyzing the performance of a sample with a more balanced ratio (41%) of left-handers than that used in other studies (<15%). We also investigated sex differences and the relationships between cognitive abilities and LRD.

We identified several task-related differences. The first was a significant impact of Orientation on the reaction time, even though we used the concrete version stimuli, which tend to reduce back/front differences (Ofte and Hugdahl, 2002b; Grewe et al., 2014). Ocklenburg et al. (2011) reported no significant differences between back and front orientation, whereas Hirnstein et al. (2011) did. This effect is most likely due to back-view stimuli being easier to process, as they do not require a mental rotation, whereas front-view stimuli usually do (Grewe et al., 2014). We also observed an impact of the number of crossings on reaction time, with a significant difference between all types of stimuli (0 vs. 1, 0 vs. 2, and 1 vs. 2 crossings). Ocklenburg et al. (2011) described a similar effect but did not find a significant difference between no crossing and one crossing. This is also related to the difficulty of the task, increasing along with the number of crossings (Ofte and Hugdahl, 2002a), thus increasing the reaction time. A congruency advantage on reaction time was found: Participants were faster to answer "True" than "False." This effect has never been described in LRD research but exists with the same magnitude (250–300 ms) in some other tasks, such as number categorization with Yes/No answers (Sheridan and Flowers, 2010), numerical reasoning questions (Vamvakoussi et al., 2012) or True/False classification of objects' properties (Collins and Quillian, 1969), with a faster reaction time for True/Yes over False/No. Thus, this confirmation bias does not appear specific to the task but supports the observation that it is easier to confirm than to deny a proposition, whatever the task.

In agreement with previous reports, we found no main effect of handedness on LRD performance (Ofte, 2002; Gormley et al., 2008; Grewe et al., 2014; Slagman, 2014; McKinley et al., 2015). However, we unraveled an interaction between handedness and the target hand's laterality. Although right-handers showed no significant difference between any of the conditions, left-handers were better and faster at identifying left target-hands than right target-hands. Interestingly, this better performance of left-handers was not limited to target hands but also applied to the label itself, independently of the target hand. Left-handers were faster when the label "L," rather than "R," was presented. This is somewhat in contradiction to Marzoli et al. (2015), who found that left-handers were naturally biased toward the right arm. Our finding is also more consistent with the common-coding hypothesis (Hommel et al., 2001), which proposes that producing actions enhances the perception of related actions or actions that share features (Schütz-Bosbach and Prinz, 2007). It is noteworthy that such facilitating effects were not present in right-handers: right-handers were not faster at identifying a right hand or when a label "R" was presented. The reasons remain unclear, but one can speculate that the fact that the BLRDT bears on an allocentric perspective played a role. As a matter of fact, a comparable advantage of left-handed children over right-handed children in perceiving the left hand from an allocentric perspective has been reported earlier (Etaugh and Brausam, 1978). The authors' interpretation was that left-handed children are more aware of their handedness and seek left-handedness in others as reassurance of normality, making them more efficient at processing the concept of left. It has been further argued that laterality of others was a more distinctive trait for left-handers than for right-handers (Thompson and Harris, 1978). This observation supports that allocentric perspective would promote the salience of left-handedness in left-handers. Interestingly, in an egocentric perspective, left- and right handers showed mirrored effects. For example, it has been shown that left-handers associated positive abstract notions such as "goodness" or "intelligence" with the left, while right-handers showed the opposite pattern (Casasanto, 2009, 2011).

Women had a significantly higher error rate than men. This is consistent with the reports of several studies (e.g., Ofte and Hugdahl, 2002a; Gormley et al., 2008). It is worth noting that the effect size was small and thus likely to be sensitive to the type of LRD task used, the sampling bias and the factors included in the statistical model. However, we observed an interaction for sex and the number of crossings on reaction times, with women being slower than men as the difficulty increases. This underlines that the sex effect can be rather subtle and could depend on the type and the difficulty of the task performed (Grewe et al., 2014). The picture becomes even more complex in the present study, as a trend was found for not fully lateralized women (MPS−) to be slower than not fully lateralized (MPS−) men, independently of their handedness, as right-handed women MPS− made more errors than right-handed men MPS−. This suggests that sex may interfere with handedness. The hypothesis of reduced brain lateralization in women has been invoked to explain their lower performance (Corballis and Beale, 1970, 1976; Bakan and Putnam, 1974; Hirnstein et al., 2011). Studies have also often investigated the effect of handedness, with the same hypothesis that left-handers would have reduced brain lateralization and would be more prone to Left–Right Confusion (Brandt and Mackavey, 1981). However, several studies that included a large sample of left-handers did not show any difference in hemispheric lateralization related to handedness (Mazoyer et al., 2014; Tzourio-Mazoyer et al., 2015; Mellet et al., 2016; Biduła et al., 2017). In the same way, recent neuroimaging studies (Hirnstein et al., 2011; Hjelmervik et al., 2015) found no reason to believe that sex differences in LRD were related to a more bilateral brain in women. The fact that the effect of sex emerged through complex interaction with handedness in the present study could explain the fact that both effects are inconsistently reported in the literature.

Two domains of cognitive efficiency, namely verbal long-term memory and spatial cognition, were related to shorter reaction times. This fits with the proposition made by Benton that good performance on LRD rely on various cognitive abilities, including language (Benton, 1968). It has been shown that children with verbal learning disabilities have persistent difficulties in LRD (Cermak, 1984), but to our knowledge, this is the first time that a relationship between proficiency in LRD and verbal memory is reported in adults. The implication of a verbal memory component in LRD supports previous results showing that LRD bears on verbal labeling rather than on perceptual encoding (Sholl and Egeth, 1981). Those results emphasized that the association between words and directions is crucial for the emergence of the concept of left and right. Accordingly, it has been shown that students who used specific non-verbal strategies to discriminate left from right (referring to their writing hand, for example) exhibited poorer performance on BLRDT than students who did not rely on any technique (Gormley et al., 2008). An advantage of verbal strategy has also been reported in the practice effect of BLRDT (Grewe et al., 2014). Our results suggest that the association of the words left and right to the corresponding concepts may be more robust and more easily accessible for people with good verbal long-term memory.

Spatial cognition was the other cognitive component related to LRD performance. This finding could appear to contradict some previous studies that reported the absence of relationships with mental rotations or maze tests (Jordan et al., 2006; Ocklenburg et al., 2011). However, it worth noting that the spatial cognition component of the present study represented abilities in processes common to mental rotation, navigational tasks, short-term spatial memory, and spatial reasoning. The association between BLRDT and this component does not extend to each test individually. Accordingly, the reaction times to BLRDT were not associated with the Mental Rotations Test (p = 0.45), and the association with the Maze test was only marginal (p = 0.08), which is in line with previous reports. Overall, our results suggest that speed performance on BLRDT rely on the fluid aspects of spatial cognition, including executive function, effortful control, and working memory capacity rather than on the specific abilities assessed by each test. This also fits with the proposition that the decline in performance on the BLRDT test observed among elderly participants corresponds to a general cognitive decline rather than being related to specific visuo-spatial operations (Ofte and Hugdahl, 2002a).

It has previously been shown that participants with a bilateral hemispheric involvement in a language production task scored lower than participants with a typical leftward dominance in various cognitive tests, including visuo-spatial assessments (Mellet et al., 2014b). One might speculate that left–right discrimination might be another illustration of this phenomenon. One could indeed relate the hemispheric lateralization for language with performance in BLRDT with participants having the lower score to BLRDT being those with the less pronounced leftward lateralization for language. However, testing this hypothesis would require a large number of participants because this effect, although obvious, was weak (Mellet et al., 2014b).

CONCLUSION

Due to this study's balanced ratio in handedness and sex, we showed an interaction between sex and manual preference, thus providing new insights into the characterization of left–right discrimination variability. We also found a significant advantage of left-handers for the concept of left, whether we tested hand laterality or the label. Finally, an extensive assessment of cognitive abilities allowed us to show that independent of sex, high spatial and verbal long-term memory abilities increased the speed, but not the accuracy, of LRD.

AUTHOR CONTRIBUTIONS

EM designed the study. MC performed the experiments. MC and EM analyzed the data and wrote the article.

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Spatial Alignment and Response Hand in Geometric and Motion Illusions

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Perception of visual illusions is susceptible to manipulation of their spatial properties. Further, illusions can sometimes affect visually guided actions, especially the movement planning phase. Remarkably, visual properties of objects related to actions, such as affordances, can prime more accurate perceptual judgements. In spite of the amount of knowledge available on affordances and on the influence of illusions on actions (or lack of thereof), virtually nothing is known about the reverse: the influence of action-related parameters on the perception of visual illusions. Here, we tested a hypothesis that the response mode (that can be linked to action-relevant features) can affect perception of the Poggendorff (geometric) and of the Vanishing Point (motion) illusion. We explored the role of hand dominance (right dominant versus left non-dominant hand) and its interaction with stimulus spatial alignment (i.e., congruency between visual stimulus and the hand used for responses). Seventeen right-handed participants performed our tasks with their right and left hands, and the stimuli were presented in regular and mirror-reversed views. It turned out that the regular version of the Poggendorff display generates a stronger illusion compared to the mirror version, and that participants are less accurate and show more variability when they use their left hand in responding to the Vanishing Point. In summary, our results show that there is a marginal effect of hand precision in motion related illusions, which is absent for geometrical illusions. In the latter, attentional anisometry seems to play a greater role in generating the illusory effect. Taken together, our findings suggest that changes in the response mode (here: manual action-related parameters) do not necessarily affect illusion perception. Therefore, although intuitively speaking there should be at least unidirectional effects of perception on action, and possible interactions between the two systems, this simple study still suggests their relative independence, except for the case when the less skilled (non-dominant) hand and arguably more deliberate responses are used.

Keywords: Poggendorff illusion, Vanishing Point illusion, hand actions, spatial alignment effect, hand dominance, attentional dominance

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INTRODUCTION

In everyday life, we are often exposed to stimuli which might be misleading, or result in apparently incoherent and sometimes unstable perception of visual illusions (Gregory, 1997). Our visual systems interpret these stimuli based on the available cues in the environment and standard internal processing mechanisms, instead of relying merely on objective physical properties of objects (Hoffman, 2005). Therefore, studying visual illusions can be a powerful tool to gaining insights into the properties of the visual system (Eagleman, 2001; Scocchia et al., 2014).

Visual illusions have also been used to show that perception can sometimes influence action. For instance, illusions can affect action parameters like grip aperture when objects are placed in the configuration of a visual illusion (Milner and Dyde, 2003; Gonzalez et al., 2006; but see Van Der Kamp et al., 2012). In particular, the left hand is influenced to a greater extent by visual illusions than the right hand (Gonzalez et al., 2006). In a similar vein, the non-dominant hand is more prone to the size weight illusion (i.e., smaller objects perceived as heavier) when used to grasp and lift up objects (Buckingham et al., 2012).

Importantly, this influence of perception on action is especially seen at early stages (i.e., movement planning). For instance, during actions, congruency between the hand used and the position of the stimuli results in a facilitation effect, in other words in faster actions (De Stefani et al., 2014). On the contrary, incongruence between the hand used and the spatial position of the visual stimulus (right hand – stimulus on the left) results in an interference effect, with participants taking more time to plan and consequently to perform an action (De Stefani et al., 2014). This phenomenon is known as the spatial alignment effect, and affects human perception and performance as shown by the well-known Simon Effect (Simon and Wolf, 1963; Simon and Rudell, 1967), where responses are more accurate and reaction times faster when the stimulus appears at the same relative location as the response. Other instances of the importance of spatial alignment in human performance have been provided by evidence of facilitation in the identification of haptic stimuli by blindfolded observers facing the stimuli rather than orthogonally to them (Scocchia et al., 2009). Furthermore, visual properties of objects that are useful to plan movements are processed well in advance before execution. This is the case of affordances (Tucker and Ellis, 2004). When seeing a cup of coffee with the handle oriented in a graspable position, we are faster in both – deciding to act upon as well as executing the real movement. In a similar vein, a model trying to explain the influence of visual illusions on actions (Glover, 2002) claims that when individuals are planning a movement, influence of illusions is greater than during online control of movements, paralleling the effect seen for affordances.

Interestingly enough, the ample discussion on the influence of illusions on actions (Carey, 2001) has not been followed by the reverse: do action related properties, usually taken into account when planning a movement (even in the absence of the real movement), influence perception? One prediction that follows from the interplay between action and perception is that such an effect should be visible even when no "real action" takes place, such as in a simple adjustment task requiring a keyboard or mouse response. Even in this case, visual properties that are related to affordances should affect perception (Glover, 2002; Borghi, 2004; Tucker and Ellis, 2004). Importantly, this would suggest that the action-perception modulation in the case of illusions is bi-directional.

To shed light on this hypothesis, we explored if perception of the Poggendorff (geometric illusion) and of the Vanishing Point (VP) illusion (motion illusion) is affected by two parameters that commonly influence action planning: the hand of response and stimulus spatial alignment. The first one was picked because of its well-documented connection with perception. The second one was used because of its effect on action performance (Whitney et al., 2003). Importantly, the Poggendorff illusion significantly activates areas that are related to action and not only areas related to perception: the left premotor cortex and the left inferior frontal cortex (Shen et al., 2016). The premotor cortex is known to be involved in transforming the spatial features of perceptual stimuli into sensorimotor information useful for the action system (Shen et al., 2016). On the other hand, perception of motion, real or illusory, is related to visual activity in early occipital as well as higher-order temporal areas, which contribute more to perception than action planning (Newsome and Paré, 1988; Tootell et al., 1995).

As mentioned above, we used a simple adjustment task requiring a keyboard or a mouse response as the aim of our study is to investigate the effects of response mode (and, putatively, the impact of the mechanisms that can be critical for action planning) on perception, when no target-related action is really performed. The adjustment task has been adopted as a comparison task to a grasping task commonly used in previous studies on the influence of visual illusions, or lack of thereof, on action performance (Aglioti et al., 1995; Franz et al., 2000, 2003). Despite its motor component, this task is driven by conscious perception of a perceptual criterion rather than by biomechanical constraints or physical parameters differently from a complex movement in which the target object properties, such as size or orientation, are processed in relation to the limb performing the action (Goodale et al., 2005, 2008).

Different predictions follow the described hypothesis. Firstly, if action influences perception, hand dominance (using the left or the right hand to respond) as well as hand and spatial-alignment interactions (visual stimulus – hand congruence) might lead to different magnitudes in illusion perception (Carey, 2001). This prediction follows from previous studies in which illusions influenced more the left hand in both right and left handers (Gonzalez et al., 2006; Buckingham et al., 2012). Similarly, studies on visual affordances of objects suggest that congruency leads to a greater precision when performing a movement (Sartori et al., 2011). Translating this into illusions, one could predict a more accurate performance, in other words a smaller magnitude of the illusion, for the congruent configuration. On the other hand, if action does not influence perception, hand dominance and spatial alignment should not modify perception of illusions, suggesting a uni- rather than a bi-directional modulation.

MATERIALS AND METHODS

Participants

Seventeen naïve participants took part in this experiment (10 males, average age and standard deviation = 29.8 ± 9.7 years). All participants were recruited at the School of Social Sciences (Psychology Department) at

Heriot-Watt University (Edinburgh, United Kingdom). Only right-handed participants were enrolled in this study to avoid interferences related to brain lateralization (Ionta and Blanke, 2009). The Edinburgh Handedness Inventory – short form (Veale, 2014) was used to assess handedness, with a cut off to discriminate right handed participants of 61 (Veale, 2014). All participants had normal or corrected to normal vision and were right-handed (average laterality quotient 91/100; range: 62.5–100). Finally, participants had no history of neurological or psychiatric conditions, either chronic or degenerative, and no drug or alcohol abuse or treatment.

The study followed the guidelines of the Declaration of Helsinki and was approved by the local Ethical committee (Approval number: 2015-130). Before taking part in the study, each participant signed the informed consent and agreed to participation. The protocol was approved by the School of Life Sciences Ethic Committee.

Stimuli

Poggendorff Illusion

The Poggendorff illusion is a geometrical illusion in which two collinear oblique line segments, which are separated by two vertical lines, are perceived as misaligned. In our stimuli (**Figure 1A**), the oblique line segments were black and measured about 1.7 cm each in length and 0.03 cm in width; they were separated by a light-gray rectangle (4.1 cm × 2.2 cm) and, therefore, in a horizontal dimension the stimulus subtended a visual angle of around 5.35 degrees. The line segments and the rectangle were presented in a 5.4 cm × 5.4 cm white inset on a gray background: the lower basis of the rectangle laid on the edge of the inset, bordering with the gray background. The stimuli were centered on the screen center.

Vanishing Point Illusion

The VP illusion is a visual phenomenon in which participants perceive the location where the stimulus (a dot) disappears to be displaced forward to its real position, in the same direction of the stimulus movement. In our protocol, a blue dot (diameter: 0.2 cm) (**Figure 1C**) was displayed on a black background and translated horizontally, from left to right (regular condition) or from right to left (mirror condition). Its velocity was about 9 cm/s and the length of its trajectory was 3.5 cm and, therefore, in a horizontal dimension the subtended visual angle of the displacement was around 3.99 degrees.

Mirror Versions of the Tasks

The mirror versions of our illusory displays were the same stimuli as described above but presented to the observer in reversed views (**Figures 1B,D**). For the Poggendorff Illusion, participants aligned the left line segment with the right line segment and for the VP participants saw a blue dot moving from the right side of the screen to the left side. The procedures and instructions were the same as the ones used with the regular versions of the stimuli.

Procedure

The task was administered through a custom software developed with Matlab (version R2015a for Windows) and Psych Toolbox Version 3. Stimuli were presented on a 15.6 inch laptop computer with a video card ATI Mobility^{TM} Raedon® HD 5145 with 512 MB DDR3 VRAM (resolution: 1366 × 768 pixels, refresh rate: 60 Hz).

Participants sat at a distance of about 50 cm from the screen, in a homogeneously ceiling illuminated and quiet room. During the experiment, participants were instructed to keep their posture still.

In both experiments, participants were required to perform an adjustment task, with both hands, one at the time. The starting hand in both tasks was randomized across participants.

In the Poggendorff Illusion experiment (**Figures 1A,B**), participants were instructed to adjust the position of one of the line segments by moving the up arrow key (to move the line up) and the down arrow key (to move the line down) to align the right line with the left line (regular version), or the left line with the right line (mirror version). A modified version of the PEST procedure (Taylor and Creelman, 1967) that has been described elsewhere (Scocchia et al., 2015) was employed for the adjustment task. The procedure can simply be described as follows: during the first adjustments of the right line, its position change was particularly evident. After these initial adjustments, this change progressively decreased in amplitude, up to a minimum distance of 1 pixel from the current and the previous position, and a green "traffic light" (a green circle, diameter: 0.7 cm) appeared on the left corner of the screen. When the participant saw the two lines segments as exactly aligned, he confirmed his response by pressing the space bar and proceeded to the next trial. Before a new stimulus was presented, a full screen mask composed of a white-noise luminance square distribution was displayed for 1 s. The task was composed of 12 trials, preceded by preliminary familiarization.

Given that crossing the body midline, an imaginary line that divides the body into two equal parts (Holmes et al., 2006; Ceyte et al., 2007), results in an invasion of the space of the opposite side of the body that can cause spatial interference, an external keyboard was attached to the laptop (**Figure 2**). The response keys were aligned with the body midline and participants provided their responses with their index fingers, without any crossing of the body midline.

The procedure of the VP illusion experiment is illustrated in **Figures 1C,D**. At the beginning of each trial, a white crosshair composed of two lines of about 0.35 cm × 0.03 cm intersecting at their midpoint was displayed for 0.25 s on a black screen. Participants were informed that the position of the white crosshair coincided with the starting position of the vanishing dot. The presentation position of the white crosshair varied on each trial with a random (positive or negative) jitter that could range between 0 and 0.88 cm on both the y- and the x-axis. The y-axis jitter was centered on the screen center, whereas the x-axis jitter was centered 2.5 cm to the left of the center in the regular condition and 2.5 cm to the right of the center in the mirror condition. Therefore, the vanishing dot trajectory always started to the left of the center and ended to the right of it in the regular condition. Vice versa, in the mirror condition, it started to the right of the center and ended to the left of it. After the white crosshair had disappeared, a blank black screen was displayed for

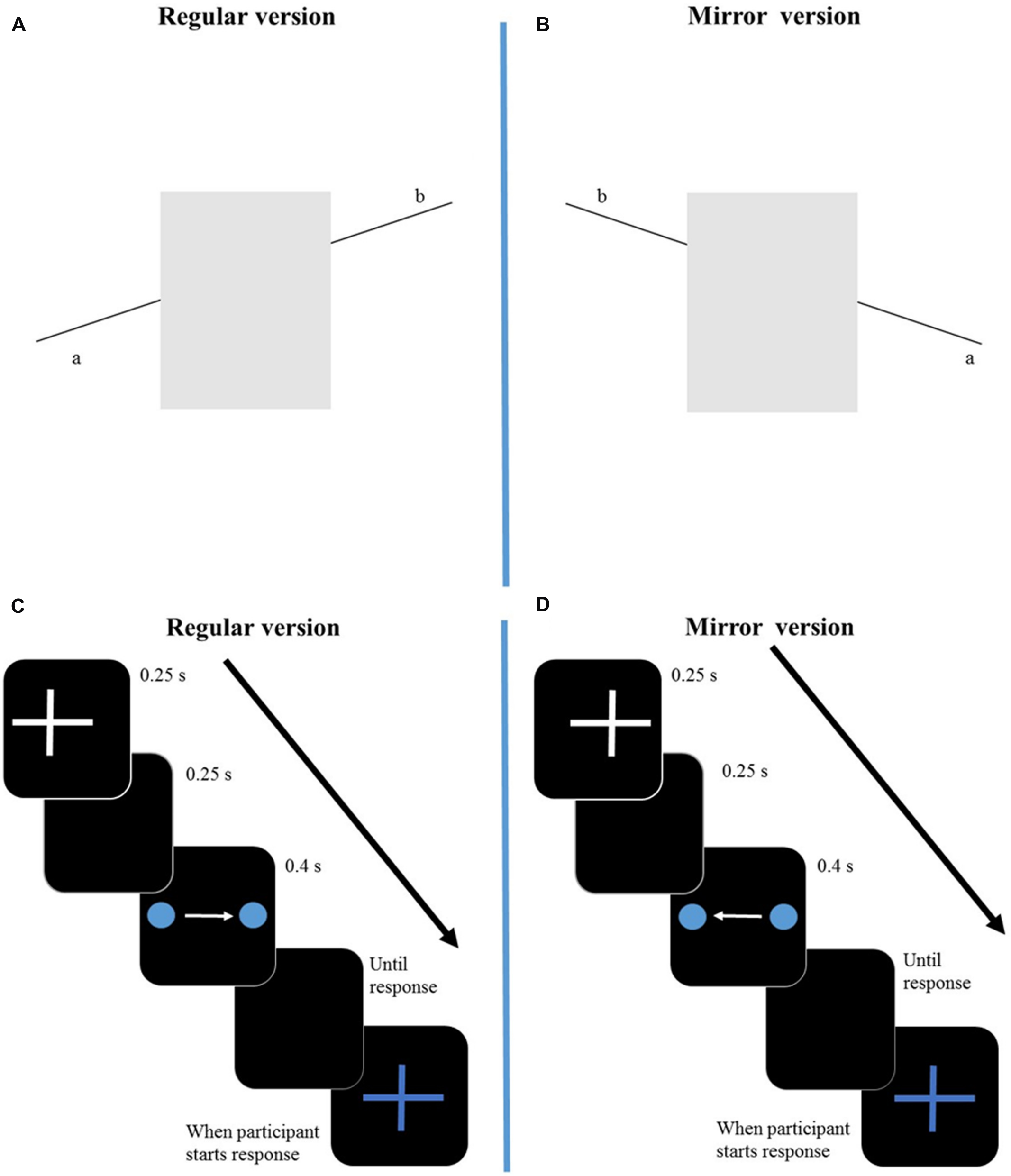

FIGURE 1 | Representation of the regular version (left side) and mirror version (right side) of the two illusions. In the regular version of the Poggendorff illusion **(A)**, participants need to align the line on the right (b) with the line on the left (a). In the mirror version of the Poggendorff illusion **(B)** participants align the line on the left (b) with the line on the right (a). In the VP illusion regular version **(C)**, the dot moves from the left side to the right side, where it disappears. In the mirror version **(D)** the dot moves form the right side of the screen to the left one. Stimuli are not drawn to scale. The arrow represents time from start of trial until participant's response. S, seconds.

0.25 s. Afterward, the vanishing dot was presented: it completed its trajectory in 0.4 s and disappeared. The blank black screen was presented until the participant moved the mouse to provide the response: at that time, a blue crosshair of the same dimensions as the starting white crosshair and of the same color as the vanishing dot was presented as mouse cursor. It was displayed only when the participant started his response movement, at a random distance in the vanishing point neighborhood (min: 1.75 cm, max: 3.5 cm, on both the x- and the y-axis, in both directions), in order to minimize external referencing to the target. Participants were instructed to place the blue crosshair exactly at the same place where they had just seen the blue dot disappear and to click the left mouse button with their index finger to record their answer. Afterward, a black blank screen was displayed for 1 s and a new trial began. The task was composed of 12 trials, preceded by preliminary familiarization.

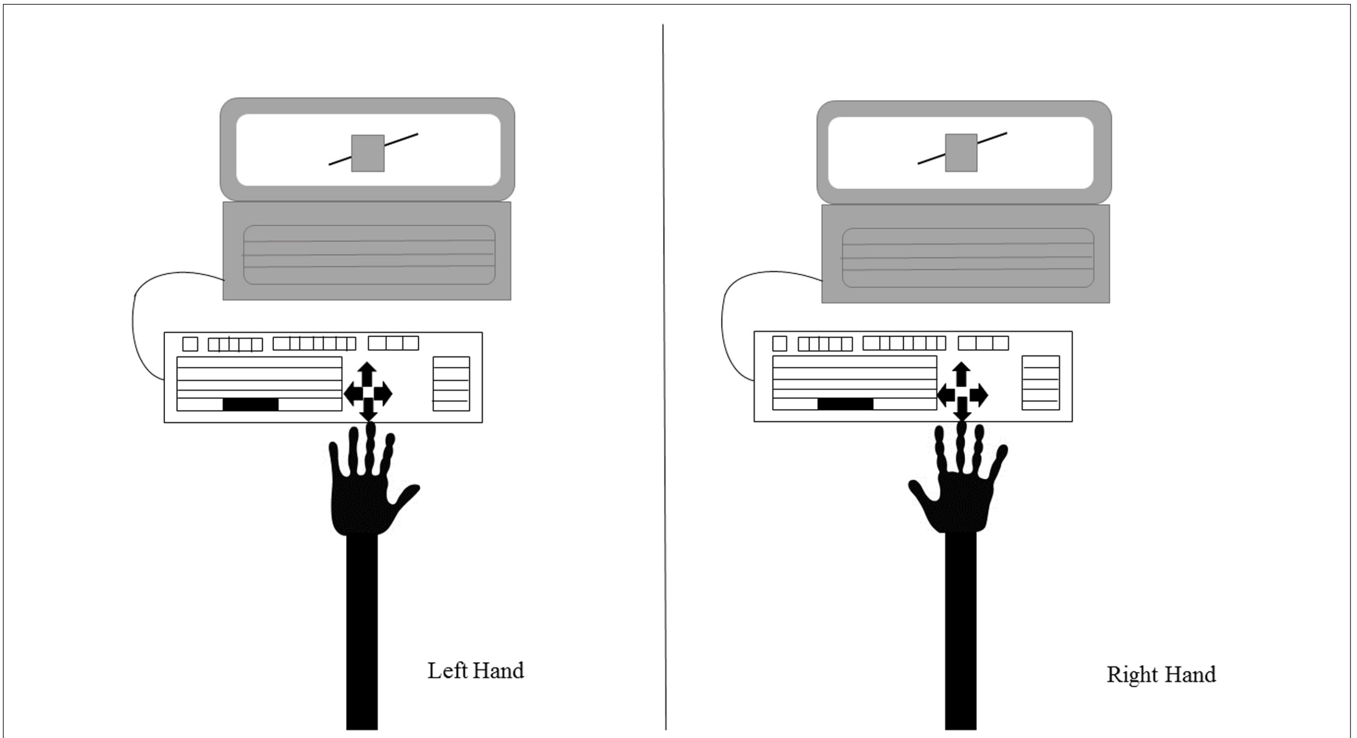

FIGURE 2 | Representation of the study setup. The participant is seated in front of the laptop showing the experimental stimuli (in this example, the Poggendorff illusion). An external keyboard is attached to the laptop to ensure the body midline is not crossed. The figure shows the keyboard and the position of the arrows used to respond: as it can be seen, this setup allows responses with both hands maintaining the same spatial alignment with the stimulus.

Data Analyses

Data have been analyzed using Matlab (Mathworks, Natick, MA, United States) and Statistica (Statsoft, Italy). A repeated measures ANOVA was conducted for both the Poggendorff illusion and for the VP illusion on two dependent measures: *illusion size* and *illusion variability. Condition* (regular, mirror) and *Hand* (left, right hand) have been introduced as within-subjects factors. Alpha level was set at 0.05. Outliers have been defined as data points below and above 2 standard deviations of the overall distribution mean, in all tasks. Partial eta squared is reported as η_p^2.

Illusion size indicates the magnitude of the perceived illusion. Thus, this variable is expressed as the individual constant error of adjustment with respect to the correct alignment for the Poggendorff Illusion or the real disappearing point for the VP Illusion. The average distance between the participant's and the correct response is computed in pixels using the 12 trials composing both the experiments.

Illusion variability is the variable error of adjustment. This variable refers to the individual responses standard deviation (set of 12 trials), and allows to measure variability in perceiving the illusion (i.e., the greater the variability, the less homogeneous the responses).

For the VP illusion, the variables have been separately analyzed for the displacement on the *y*-axis (gravitational error) and for the displacement on the *x*-axis (horizontal displacement error).

RESULTS

Poggendorff Illusion

Data processing resulted in removing 44 outliers across all the different conditions, in other words 5.39% of the total data points. We found a main effect of Condition [$F_{(1,16)} = 10.53$; $p = 0.005$; $\eta_p^2 = 0.39$] showing that the regular version of the Poggendorff illusion generates a stronger illusion compared to the mirror version (**Figure 3**). No other main effects [Hand: $F_{(1,16)} = 0.65$; $p = 0.433$] or interactions [Hand by Condition: $F_{(1,16)} = 0.26$; $p = 0.614$] have been found. No significant effects have been found for illusion variability [Hand: $F_{(1,16)} = 0.305$, $p = 588$; Condition: $F_{(1,16)} = 1.83$, $p = 0.196$; Hand by Condition: $F_{(1,16)} = 0.587$, $p = 0.455$].

Vanishing Point

Gravitational Error (*Y*-Axis)

We removed 26 outliers across all the different conditions, in other words 3.18% of the total data points. We found a main effect of Hand for both illusion size [$F_{(1,16)} = 7.034$; $p = 0.017$; $\eta_p^2 = 0.30$] and illusion variability [$F_{(1,16)} = 5.134$; $p = 0.038$; $\eta_p^2 = 0.24$]. Both effects show that participants are less precise and more variable when they use their left hand, independently from the illusion being a regular or mirror version (**Figure 4**). No other main effects or interactions between factors have been found [Illusion size: Condition: $F_{(1,16)} = 0.623$; $p = 0.441$, Hand

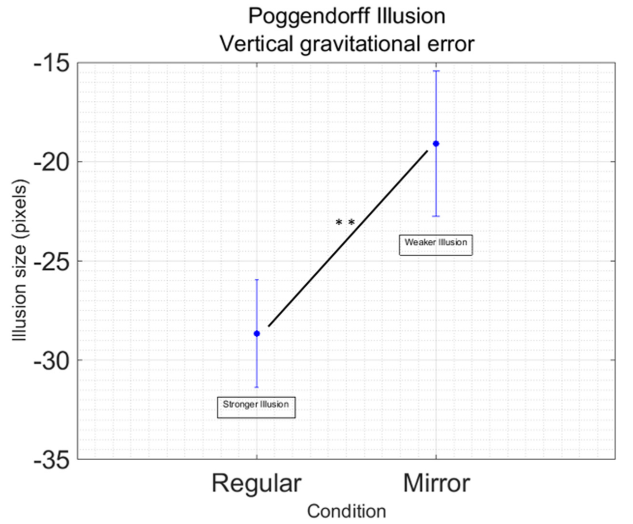

FIGURE 3 | Main effect of Condition in the Poggendorff Illusion. Data are collapsed between the right and the left hand, since this factor was not significant in the main analysis Vertical bars represent standard error of the mean. Illusion size represent the dimension of the displacement in alignment. Negative values indicate the displacement is downward. Stars indicate a significant difference at $p < 0.01$.

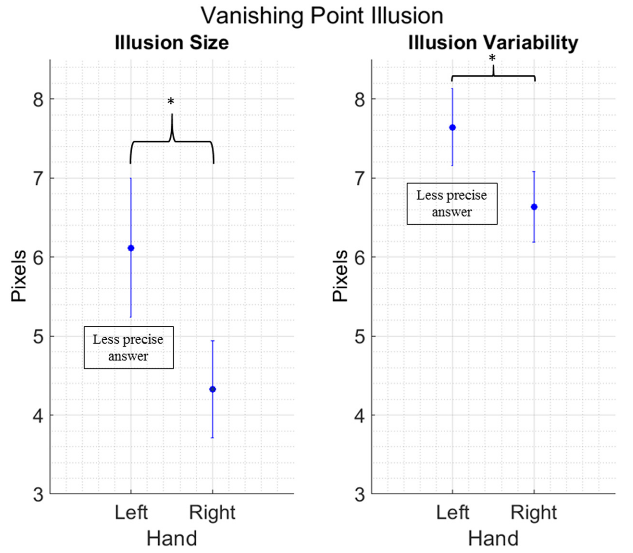

FIGURE 4 | Main effect of Hand in the Vanishing Point Illusion. Data are collapsed between the regular and mirror version, as Condition did not yield any significance in the main analysis. Vertical bars represent standard error of the mean. The y axis presents error size of the vertical gravitational error. Stars indicate a significant difference at $p < 0.05$.

by Condition: $F_{(1,16)} = 0.023$; $p = 0.882$. Illusion variability: Condition: $F_{(1,16)} = 2.550$; $p = 0.130$, Hand by Condition: $F_{(1,16)} = 0.589$; $p = 0.454$].

Displacement Error (*X*-Axis)

Data processing resulted in removing 41 outliers across all the different conditions, 5.02% of the total data points. No significant effects have been found for this measure on illusion size or variability [Illusion size: Condition: $F_{(1,16)} = 0.007$; $p = 0.933$, Hand: $F_{(1,16)} = 2.461$; $p = 0.136$, Hand by Condition: $F_{(1,16)} = 0.636$; $p = 0.437$. Illusion variability: Condition: $F_{(1,16)} = 0.184$; $p = 0.674$, Hand: $F_{(1,16)} = 0.003$; $p = 0.958$, Hand by Condition: $F_{(1,16)} = 0.005$; $p = 0.946$].

DISCUSSION

Visual illusions can be generated by different cues available in the environment, such as the geometry of an image as in the Poggendorff (Koning and van Lier, 2007) or by the perception of motion as in the VP illusion (Hubbard, 1995). Both these illusions are susceptible to changes in their magnitude depending on the manipulation of their spatial properties (Actis-Grosso and Stucchi, 2003; Actis-Grosso et al., 2008; Gallace et al., 2012). Furthermore, differences have been reported in effects between the right and the left hand when actions are directed toward targets which have perceptual illusory properties (Gonzalez et al., 2006; Buckingham et al., 2012; Van Der Kamp et al., 2012).

The aim of our study was to explore possible interactions between the response mode (here: the acting hand – right vs. left) used to adjust or indicate target locations, and the arrangement of the illusory displays (regular vs. mirror reversed). Previous studies explored the effects of illusions on action, and often reported lack of thereof, but not the reverse (Goodale et al., 2008). One could hypothesize some modulatory effects of action undertaken to respond in a task on the perception of illusions themselves given the examples from the perceptual domain, such as the case of affordances, where action related properties of seen objects affect processing velocity even in absence of a real action (Glover, 2002; Borghi, 2004; Tucker and Ellis, 2004). We explored if the compatibility between the hand and the target part of the illusory stimulus has a role in reporting the extent of geometric and movement related illusions. More specifically, healthy participants were shown the Poggendorff (geometric) illusion and the VP (motion related) illusion, both in a regular and mirror version, and were asked to reply using either their right dominant or their left non-dominant hands.

Our findings show a different pattern of responses in the contexts of geometric- and motion-related illusions. The response mode did not play a role in the Poggendorff illusion. Yet, in the VP illusion, participants show more variability in reporting the illusory target location, making greater gravitational errors (displacements on the *y*-axis) when they use the left hands. This latter outcome is consistent with previous studies showing greater influence of illusory displays on the responses performed with the left (but not right) hands (Gonzalez et al., 2006; Buckingham et al., 2012), as opposed to revealing no differences between hands (Van Der Kamp et al., 2012). In our case, one could speculate that using the left hand makes a right-handed participant less accurate and increases the illusion size. However, the effect is somewhat spurious and likely related to the poorer motor control of their non-dominant (and less trained) left effector, as not only the performance accuracy, but also its precision is lower with the left hand, indicating an increase in response variability. Put it differently, the variable error, and not only the constant error, increments when participants provide their response with their non-dominant hand. As such, it seems more conservative to ascribe the results on illusion size to the participants' tendency to shift their responses toward the bottom part of the screen (due a poorer control of the effector), rather than to a perceptual phenomenon. Secondly, for this illusion, the hand effect emerges independently form the direction of the movement being from left to right or from right to left. In other words, the spatial alignment does not affect illusion susceptibility in this motion illusion. Given that perception of motion related illusions may rely on early visual (occipital), as well as higher-order (temporal) areas, which contribute more to perception than action planning, one could conclude that action related parameters do not affect these types of illusions (Newsome and Paré, 1988; Tootell et al., 1995).

In the Poggendorff illusion, we found that the regular version generates a stronger effect, independently from any spatial alignment. Spatial alignment is seen when the hand giving the response is lateralized to the same hemifield where the stimulus is presented (i.e., left hand and left hemifield). As such, one would expect an interaction between Condition and Hand to confirm this effect. However, we only found an effect for Condition, meaning that the congruency/incongruence between the hand and the visual field does not play a role. In other words, the oblique line placed on the right side of the figure elicits a greater illusory displacement in the Poggendorff display and this is true independently from the hand used: the oblique line located on the right side of the space still generates a bigger effect even when the answer is given with the left hand. This pattern is similar to what has been previously found for the Müller-Lyer illusion, which equally impacts movement parameters of both grasping hands (Van Der Kamp et al., 2012).

Several explanations have been put forward to account for the Poggendorff illusion. For instance, the role of perceived angles formed by the oblique line encountering the parallel line (Greene, 1987) and the perceptual distortion of space between the parallel lines have been discussed (Greist-Bousquet and Schiffman, 1981). Importantly, our experimental design allows to rule out that performance in our regular and mirror Poggendorff illusion differ due to differences in the perceived angles (as they have the same acuteness in both versions) or from a distortion of the occlusive rectangle (which is the same in both conditions). Accordingly, space geometry (in particular spatial anisometry) appears to have a greater influence on the Poggendorff illusion perception than any spatial compatibility or hand effect. Asymmetries in attention direction are assumed since the first models, developed to explain neglect, in which the Authors describe two attentional vectors with a left hemispheric vector being stronger than the right one (Kinsbourne, 1970). Similarly, Corbetta et al. (1993) propose a dominance for the right hemisphere that guides attention toward both hemispaces, while the left one only toward the right hemispace. All these models, in different ways, suggest an advantage for the right hemispace that we show for the first time also for illusions, in which the target stimulus elicits a greater magnitude of the illusion when located in the right visual field. Attentional attraction toward this side of space appears to increase the perception of the illusion through anisometric perception mechanisms. Future studies could rule out if this is related to a right–left anisometry or a directional anisometry, as both explanations are possible. In other words, whether the oblique line to be adjusted is located on the right side of space might influence our ability to align it, causing a distortion of perceptual information that further increases the illusion size. This might not be the case if the line is on the left – where our perceptual system can follow a classic left-to-right direction of visual exploration – and as such might not be affected by anisometry (vertical axis anisometry). Another possibility is that oblique lines located in the right hemifield cause a directional bias as they "point" toward the lower part of the visual filed (assuming visual scanning starts from the left), while the line located in the left side of space in the mirror version points toward the upper part of the figure (top-down axis anysometry). In any case, it is relevant to highlight that visual setups taking into account attentional phenomena could prove helpful to understand illusions perception, as disagreement between theories might be due to the lack of proper manipulations that allow to weight the contribution of cognitive functions other than perception to these phenomena.

Independently from the explanation of the increase in illusion size observed in the regular versus mirror version of the Poggendorff illusion, our findings confirm that parameters taken into account when planning a "response action" do not affect perception of this illusion, suggesting lack of direct influences of perception on action, or vice versa.

In summary, our results do not support the idea that action parameters involved in reporting (or adjusting) illusory distortions, that might be also relevant for the planning of motor responses in general, can influence the magnitude of the perceived visual illusions. This result challenges the idea that similar visual representations are shared even in an initial stage of perception *per se* and planning of relevant actions (Glover, 2002). While the idea of an influence (at least to some extent) of perception on action planning holds (Carey, 2001), the reverse cannot be confirmed, at least by our experimental manipulations. Bruno (2001) exploring the discrepant results on visual illusions and action, asks "Even if dissociable at some stage, visual perception and visually planned action must coordinate at some other stage. Which one and where?" Our findings suggest that this coordination does not happen at an early stage, where independence can be seen between the two processes.

Although only right-handed participants were tested in this study to avoid any interference from possible changes in the lateralization of functions in the brain (Ionta and Blanke, 2009), the reports by Gonzalez et al. (2006) and Króliczak et al. (2016) suggest that the outcomes should not be that different for left-handers. After all, the majority of them (around 70%) should have higher-order praxis skills lateralized similarly to right-handers (Króliczak et al., 2011; see also Corballis, 2017). It is tempting to say, though, that the results obtained from the remaining 30% of left-handers could be substantially different. Such participants should be of interest for any laboratory that could selectively target such a sample of individuals in their research.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: LS and AS. Performed the experiments: MP. Analyzed the data: LS. Contributed reagents/materials/analysis tools: NS and LS. Wrote the paper: LS, MP, NS, and AS.

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Is there a Competition between Functional and Situational Affordances during Action Initiation with Everyday Tools?

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Most studies of human-tool interactions focus on the typical use of a tool (e.g., cutting in the case of a knife). However, little is known about situations requiring atypical tool use (e.g., using a knife to tighten a screw). The present study focused on a selection of atypical uses of everyday tools which might be in conflict with their typical use. Our objective was to study how tool function influences the selection of the relevant action. In Experiment 1, which involved visuomotor priming, two everyday tools (a knife and a screwdriver) and two neutral tools (two bars, with no strong functional affordance) were used as primes and targets. Participants had to use the target with the appropriate box (indicated by the color) that allowed to make an action. Longer initiation times were observed when the prime was an everyday tool, irrespective of the nature of the target. We therefore observed a conflict between functional and situational affordances. To investigate whether the priming effect is caused by the task-irrelevance of the prime, we asked the participants in Experiment 2 to perform an action associated with the prime. The results showed longer initiation times only when the prime and target were everyday tools, irrespective of their precise nature. This suggests that activation of the typical use of a tool might not be fully automatic but flexible depending on the situation.

Keywords: visuomotor priming, tool use, tool function, atypical tool use, affordance

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INTRODUCTION

Throughout our lives, we interact with many tools in the same way to achieve the same goals (e.g., cutting food with a knife). These experiences allow us, among other things, to construct semantic/functional knowledge about tools (e.g., Buxbaum and Saffran, 1998; Borghi and Riggio, 2015). However, do we always need this functional knowledge to act with tools?

According to Gibson's (1979) theory, it is the affordances, described as opportunities for action that are directly offered by the intrinsic perceptual properties of objects, that allow us to use tools. Since these properties are invariant, the affordances do not change as a function of our needs and goals. They are directly perceived without any need to call on previous experiences with the tool and knowledge of its function. This view of affordances was modified by authors who pointed out that they are relations between one's abilities and features of the environmental situation (Tucker and Ellis, 2001; Chemero, 2003) and that they depend on previous experience and the current goal (Rosenbaum et al., 1990). Given this view, the perception of affordances depends on one's needs in the specific situation at hand as well as on the ultimate aim of the action. For example, the affordance of a knife lies in the ability to cut food at lunchtime even though it may also be used to retighten the screw of one's spectacles if needed.

Over the centuries, we have created many kinds of objects that recur consistently in our environment and lead to regular, routine actions related to their typical functions. It is very likely that this has led to us predominantly and automatically perceiving the recurrent functions of such objects. We use the term "functional affordances" to refer to this functional perception below. If we return to the example of a knife, we clearly use this object more often to cut food than to repair our glasses. However, functional affordances seem useless when a situation demands the atypical use of an object. In this case, it may be more appropriate to perceive situational affordances, which respond to the requirements of a situation and a goal that we wish to achieve. The purpose of the present study is to investigate whether functional affordances are automatically activated along with situational affordances when an atypical use of the tool is required.

Various evidence from behavioral (Derbyshire et al., 2006; McNair and Harris, 2012; Ni et al., 2014) and neuroimaging studies (e.g., Chao and Martin, 2000; Vingerhoets, 2008) lends support to the idea that humans directly and automatically perceive functional affordances in the presence of a common tool, whatever their intentions are. Visual processing of a tool is thought to be sufficient to activate the tool's affordances in a bottom-up way (Tucker and Ellis, 1998, 2001; Yoon et al., 2002; Buxbaum and Kalénine, 2010; Jax and Buxbaum, 2010; Vainio et al., 2014; Kalénine et al., 2016) independently of one's intention and the situation in which the action is performed.

Some interesting data about situation and goal-dependent affordance activation come from Jax and Buxbaum's (2010, 2013) studies with tools (e.g., a calculator) evoking two competing affordances: structural (important for grasp-to-move gestures) and functional (important for grasp-to-use gestures). Jax and Buxbaum (2010) found longer initiation times (ITs) for the conflictual objects than for the non-conflictual objects, suggesting that both affordances are activated and that one of them has to be selected, thus slowing down action initiation. In addition, patients with ideomotor apraxia have been shown to find it more difficult to grasp conflictual tools than non-conflictual ones (Jax and Buxbaum, 2013). A recent study by Kalénine et al. (2016) investigated this conflictual effect in more detail by manipulating the distance between the observer and the tools. When the conflictual tools were presented out of the reachable space, the conflict between structural and functional affordances ceased to occur. These results suggest that functional affordances might be activated independently of the task and are not dependent on the situation (Lee et al., 2013).

Because our environment is constantly changing, we often need to adapt to the specific situation and its constraints. It is therefore possible that rather than always activating the typical use of the tools, people analyze the situation and how the tool may serve their purpose. The ability to perceive the situational affordance of the tool seems particularly important for planning actions and achieving one's goal (Mizelle and Wheaton, 2010). It supports the flexibility of the human mind to achieve goals using the available resources and permits adaptation to new or unpredictable situations. In this perspective, it is the situation and the goal, not the typical function of the tool, that optimize tool use and processing (Phillips and Ward, 2002; Mizelle and Wheaton, 2010; Osiurak et al., 2010). In line with this view, it has been suggested that affordances are not automatically activated but are dependent on top-down processing determined by one's motivation and goals in any given situation (Chemero, 2003, 2013; Costantini et al., 2010; Nonaka, 2013; Osiurak and Badets, 2014) as well as by the end state of the movement (Marteniuk et al., 1987; Rosenbaum and Jorgensen, 1992; see Rosenbaum et al., 2006 for a review). This selective modulation of affordance activation by the purpose of the action may help avoid the disruptive effects of competition between functional and situational affordances (e.g., Prinz, 1997; Cisek, 2007; Hommel, 2009; Cisek and Kalaska, 2010). For example, the study by Lindemann et al. (2006) suggests that functional affordances are only activated when subjects intend to grasp the tool in a functional way, as opposed to making a finger-lifting movement. Ranganathan et al. (2011) found that ITs were shorter when subjects were asked to grasp an upright glass in the normal way or with a magnetic implement than when the glass was upside-down. This effect was not present when participants touched the glass with their fist. The authors interpreted these results as evidence that tools do not activate functional affordances automatically but instead do so in the light of the situation and the intentions of the person performing the action.

In the present study, we investigated the activation of functional and situational affordances when atypical tool use was needed. To this end, and inspired by Jax and Buxbaum's (2010, 2013) studies using tools presenting conflictual structural and functional affordances related to two different action goals (grasp-to-move and grasp-to-use) and involving different manipulations, we designed experimental material that made it possible to activate conflictual functional and situational affordances without involving different manipulations. We consequently used four stimuli: two common tools with a strong functional affordance (a knife and a screwdriver) and two control tools without any specific functional affordance (two wooden bars), together with two boxes designed to produce gestures similar to cutting and screwing, but not replicating the typical purpose of these actions. In this way, we were able, first, to control the grasp and the manipulation aspects of actions and make them as much as similar as possible for one and the same tool across different conditions, and, second, to create atypical, situational affordances. For each of the four tools, we created a new, situational affordance by associating it with a specific box having one of two colors (one common and one control tool were painted in red and were associated with a red box and the equivalent was done for a blue box). The common tools had two potentially conflicting affordances (one functional and one situational), while the control tools only had a situational affordance. In Experiment 1, we used a visuomotor priming paradigm in which the common and control tools were presented as primes and targets in order to reveal any prejudicial effect of prime processing on action

ITs for the target. The participants' task was to use the target with the appropriate box, i.e., blue target with the blue box and red target with the red box. The target color therefore indicated the goal of the action. The pairs of common tools in the prime and target formed the conflictual condition in which the functional affordance (activated by the common tool in the prime) could conflict with the situational affordance required by the task. Our hypothesis was that if functional affordances are automatically activated by the presence of a common tool, then they should conflict with situational affordances and consequently slow down the selection of the situational affordance. We therefore expected to observe longer ITs for conditions with a common tool in the prime and/or target than in conditions in which the same control tool (bar) was present in the prime and target. On the other hand, if functional affordances are not activated automatically and situational affordances are activated by the prime, we should observe faster ITs when both prime and target have the same color, independently of their identity.

EXPERIMENT 1

Method

Participants

Twenty students (16 women) from Lyon 2 University took part in the present study. Their mean age was 21.5 years (*SD* = 2.9). Participants were divided into two equal groups according to the category of tool (common tool versus control tool) used as target. All of them were self-reported as right-handed, with normal or corrected-to-normal vision. With regard to ethics, members of the laboratory gave their approval for the experiments presented in this study. In addition, prior to taking part in the experiment, the participants gave their written, informed consent in accordance with the Helsinki declaration.

Material and Stimuli

A Dell computer equipped with E-prime2^{TM} software (Psychology Software Tools, Inc., United States) was used to run the experiment and record the movement IT. The liquid-crystal goggles (Plato Translucent Technologies, Toronto, ON, Canada) used to control the subjects' vision were connected to the computer, along with a home-made, 4-cm diameter spherical release button which was used to collect the ITs. The tools used as prime and target were placed on a board 40 cm wide × 50 cm long. Two boxes were designed in order to produce gestures similar to cutting with a knife and screwing with a screwdriver (**Figure 1**). The boxes were placed at the left of the board, at a distance and angle that made it easy for the participants to interact with them. The "screwing" box was a black cube with a blue front. A piece of plastic was inserted in the middle of the front in such a way that it could be rotated in both directions. The "cutting" box was a black cube with a red front. In the middle of the front was a "Z"-shaped slit. Inside the box, there was a small horizontal platform (held in place with elastic bands) that could be reached through the upper part of the slit and moved downward along a "Z"-shaped track.

The common tools (knife and screwdriver) and control tools (bars) presented as prime and target were painted to match the colors of the boxes. The screwdriver and one bar were blue while the knife and the other bar were red. To avoid acoustic cues about the nature of the prime and target, small pieces of felt were attached to the ends of tools in contact with the experimental board.

Procedure

The participants were tested individually. They were positioned to face the experimental board, with their right hand on the release button. The primes and targets were presented on the experimental board one at a time, at a distance of about 40 cm from the participant and in front of their right shoulder. The handles of the tools were turned toward the participants and at 45° to the right of their midline. Before the experiment started, the participants were asked to get used to using the tools with the two boxes for as long as they judged necessary in order to perform the actions quickly and efficiently. The participants were divided into two groups depending on the Category of Tool used as target: common tools vs. control tools. Consequently, one group of participants saw common tools as targets and the other group saw control tools as targets. The two groups were formed in such a way that it would be easy to dissociate between possible target effects and priming effects. Each participant performed 10 training trials followed by 64 experimental trials. There were eight experimental conditions (four prime conditions × two target conditions), each of which was repeated eight times. The order of the trials was pseudorandomized across participants.

The instruction was to use the target with the appropriate box as a function of the target and box color (a blue target with a blue box, a red target with a red box). More specifically, when working with the blue box, the participants were asked to turn the middle piece 45° to the right, whereas with the red box, they were told to push the small platform down along the "Z" track. All the trials started with a "beep" to remind the participants to place their hand on the release button. At the same time, the goggles became opaque for 1500 ms, during which period a prime was placed on the experimental board. The goggles then became transparent for 500 ms so that the prime was visible, before becoming opaque again for a further 1500 ms. During the ISI, the experimenter removed the prime from the experimental board and replaced it with the target. At the end of the ISI, the goggles became transparent again and a simultaneous "go" signal indicated to the participants that they were to grasp the target as quickly as possible and use it in the corresponding box before putting it back on the board. The participants were given 7000 ms to perform the task. When the prime and the target were the same, the experimenter always displaced the prime so that the participants were not able to predict that the upcoming target was the same tool as a prime.

There were two repeated-measures factors: Target (Blue-Box-Compatible: BBC versus Red-Box-Compatible: RBC) and Prime (Common-Tool BBC – screwdriver; Common-Tool RBC - knife; Control-Tool BBC – blue bar; Control-Tool RBC – red bar); and

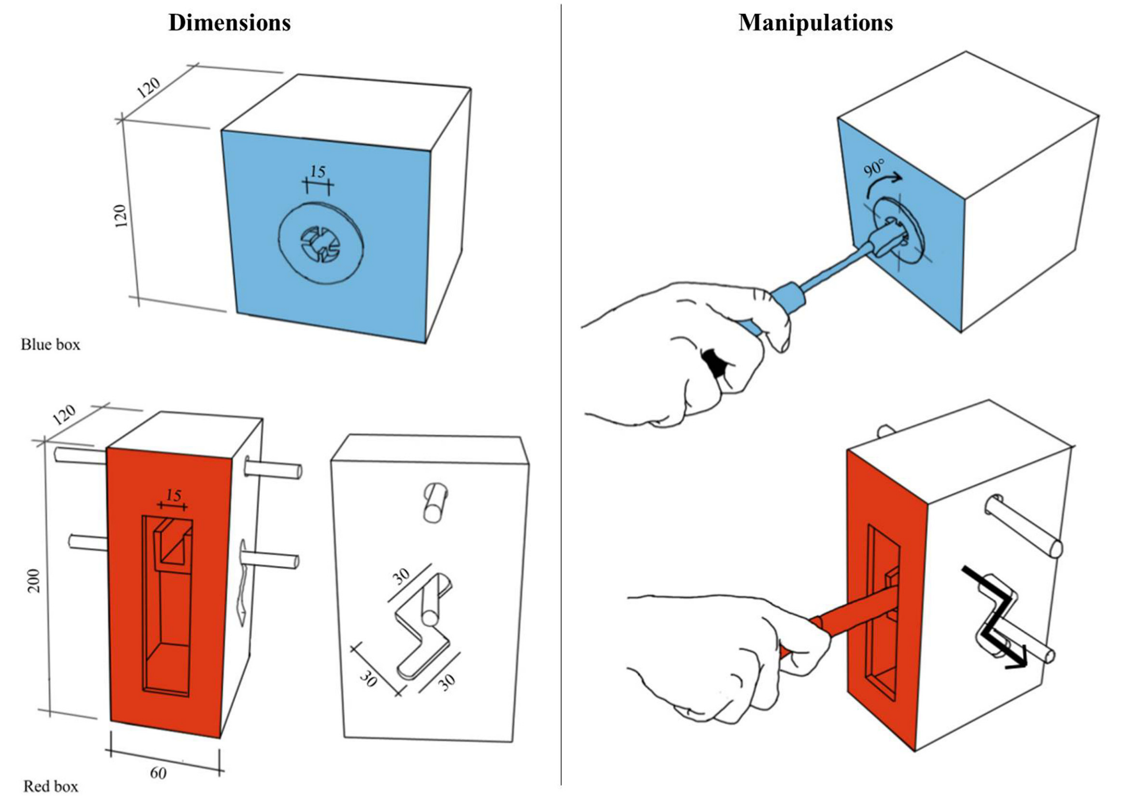

FIGURE 1 | Dimensions and manipulation associated with the two experimental boxes.

one between-subject factor Target-Tool-Category (Common-Tool versus Control-Tool). Concerning the Target factor, in the BBC condition the target was either a common or control tool to be used with the blue box (screwing action), while in the RBC condition, the target was either a common or control tool to be used with the red box (cutting action).

We measured IT as the time that elapsed between the "go" signal and the time when the participants took their hand off the release button. Preliminary analyses conducted to check for normality (Shapiro–Wilk's test) and sphericity (Mauchley's test) detected no violations. ITs above 1000 ms, below 150 ms, or differing by more than 2.5 standard deviations from the individual mean for each condition were removed (less than 2% of the data). A mixed-measure ANOVA was performed with one between-subject factor: Target-Tool-Category and two within-subject factors: Target and Prime. A significance level of $a = 0.05$ was used for all statistical analyses. The participants performed the task accurately, with an overall accuracy rate of 96.5%. For control purposes, we checked for a possible difference between the two boxes, but found no significant difference.

Results

The ANOVA showed a significant effect of the Prime [$F(3,54) = 3.74$, $p < 0.02$, $\eta^2 = 0.17$; **Figure 2**]. Planned comparisons revealed significantly longer ITs after the presentation of common tools than control tools in the prime. More precisely, the IT was longer after common RBC primes than after control RBC primes ($p < 0.04$) and marginally longer than after control BBC primes ($p = 0.07$). Similarly, the IT were significantly longer after common BBC primes than after control BBC primes ($p < 0.05$) and control RBC primes ($p < 0.04$). There was no other significant difference.

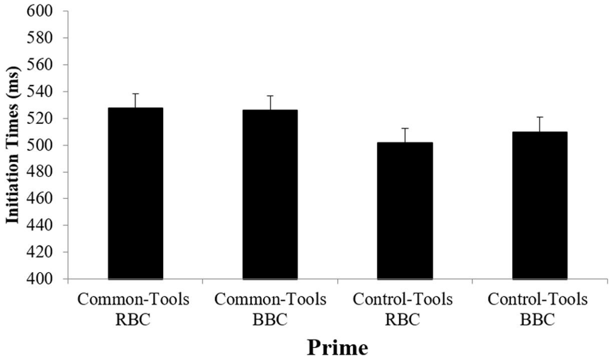

FIGURE 2 | Mean Initiation Times (ITs) as a function of Prime condition: common tool RBC, common tool BBC, control tool RBC and control tool BBC. Error bars represent 95% within-subject confidence intervals.

The other effects and interactions were not significant. More specifically, the simple effects of Target [$F(1,18) = 2.13$, $p = 0.16$]

and Target-Tool-Category [$F(1,18) = 0.22$, $p = 0.64$] and the Prime*Target [$F(3,54) = 0.84$, $p = 0.47$], Target*Target-Tool-Category [$F(1,18) = 2.12$, $p = 0.16$], Prime*Target-Tool-Category [$F(3,54) = 1.71$, $p = 0.17$] and Prime*Target*Target-Tool-Category [$F(3,54) = 0.29$, $p = 0.82$] interactions were not significant.

Discussion

In Experiment 1, we formulated two alternative hypotheses. One was that if the activation of affordances depends on the requirements of the situation and the individual's goals, then functional affordances should not be activated automatically. Instead, only situational affordances should be activated. Consequently, shorter ITs should be observed when prime and target share the same color. Our results do not support this hypothesis as we did not observe significantly shorter ITs in these conditions. Indeed, the interaction between prime and target was not significant, indicating that action ITs were not faster when the prime and target were compatible (e.g., red bar in prime and target, knife in prime and target).

The second hypothesis was that functional affordances are activated automatically independently of the situation and the participants' goals. This hypothesis led to the prediction of longer ITs for conditions with a common tool as prime because common tools should activate both functional and situational affordances, and functional affordances should therefore compete with situational affordances, thus slowing down action ITs. In accordance with this prediction, the results showed longer ITs when common rather than control tools were presented as primes, irrespective of the target category (common or control tool) and prime-target compatibility. This might suggest that seeing a common tool in the prime automatically activates its functional affordance and influences the processing of the target, even if the function of the tool is irrelevant to the situation. Our data are consistent with Lee et al.'s (2013) and Kalénine et al.'s (2016) observations suggesting that functional affordances may be activated automatically.

It might be expected that if functional affordances are activated automatically then seeing a common tool as a target should also have some prejudicial effects on the time of action initiation because, in this case, functional affordances might compete with situational demands. However, our data do not indicate such disruptive effects given that we did not observe any significant effect of Target-Tool-Category or any significant interaction of this factor with Prime. The ITs were not significantly longer when the target was a common tool as compared to a control tool in any of the prime conditions. In particular, our results indicate that the conflict between functional and situational affordances was not greater for a condition in which the tool was the same in the prime and target. It is possible that functional affordances were automatically and predominantly activated when common tools were presented as the prime because the participants did not have to perform an action in response to the prime and processing of the prime, which was irrelevant to the task, was not influenced by the participants' goals and intentions. However, when we consider the tools presented as the target, which were relevant for the task because the participants were asked to use them, there was no automatic activation, because it was counteracted by the situation-dependent processing of task-relevant information. Thus, when the situation requires an atypical, situational use of a tool, the functional affordance is probably not activated sufficiently to interfere with the more highly activated required situational affordance. On the other hand, it could be argued that if situational affordances are activated only when they are task-relevant, it is possible that they are not activated during the processing of the prime because, as we have already said, the participants did not have to perform any action with the prime. To test this idea, it would be possible to ask the participants to perform an action using the target as if it were the tool seen in a prime. Thus, in Experiment 2, we used a protocol similar to that used in Experiment 1 and we asked the participants to use the target in the same way as if it were the prime they had just seen. Our prediction was that if the activation of functional affordances is counteracted by that of situational affordances then the ITs should be shorter for common tools when the prime and target share the same color. This should also be the case for control tools because they only activate situational affordances.

We also formulated an alternative prediction. According to the view that the dominance of functional affordances means that they should be automatically activated whatever the situation, longer action ITs should be observed when common tools are presented as primes, and especially when both prime and target are common tools. In this case, functional affordances would enter into competition with situational affordances.

EXPERIMENT 2

Method

Participants

Twenty students (15 women) from Lyon 2 University took part in the present study. Their mean age was 22.6 years (*SD* = 2.7). All of them were self-reported as right-handed, with normal or corrected-to-normal vision. Prior to taking part in the experiment, the participants gave their written, informed consent in accordance with the Helsinki declaration. The participants were divided equally into two groups depending on the nature of the prime (common and control tools).

Material and Stimuli

The same material and stimuli were used as in Experiment 1.

Procedure

The procedure was similar to that used in Experiment 1. However, each group of participants was presented with only one type of prime (common or control tool). In this experiment, the participants were instructed to use the target. However, the way in which they used it was determined by the prime. Thus, for example, if the prime was a common tool to be used with the blue box (screwdriver), then the target had to be used as a screwdriver with the appropriate box (blue box) irrespective of whatever it actually was (knife, screwdriver, red or blue bar). The four tools were presented as targets.

A mixed-measures ANOVA was performed, with a between-subject factor: Prime-Category (Common Tool vs. Control Tool) and two within-subject factors: Prime (Blue-Box-Compatible: BBC vs. Red-Box-Compatible: RBC) and Target (Common-Tool BBC – screwdriver; Common-Tool RBC - knife; Control-Tool BBC – blue bar; Control-Tool RBC – red bar).

The participants performed the task accurately, with an overall accuracy rate of 94.2%. For control purposes, we checked for a possible difference between the two boxes, but found no significant difference.

Results

The ANOVA showed no significant simple effects and no significant interactions (all $p > 0.1$), except for the interaction between Prime Category and Target [$F(3,54) = 4.36$, $p < 0.01$, $\eta^2 = 0.19$; **Figure 3**]. Planned comparisons showed that when the primes were common tools, ITs were significantly longer for common tool than for control tool targets. More precisely, longer ITs were observed for common RBC targets (mean = 551 ms) than for control RBC targets (mean = 504 ms; $p < 0.04$) or for control BBC targets (mean = 500 ms; $p < 0.05$). Similarly, common BBC targets (mean = 534 ms) had longer ITs than control BBC ($p < 0.02$) and control RBC cargets ($p < 0.01$). There was no significant difference between common BBC targets and common RBC targets ($p = 0.23$) or between control BBC targets and control RBC targets ($p = 0.62$). No significant differences were observed in the action ITs when control tools were presented as primes between the different target conditions.

In addition, we looked at differences between the prime categories (common vs. control tools) for each target condition. Comparisons revealed marginal differences for both common tools (RBC: $p = 0.07$; BBC: $p = 0.08$) and no significant difference for control tools (RBC: $p = 0.44$; BBC: $p = 0.44$).

Discussion

In Experiment 2, we formulated two alternative hypotheses. The first posited that situational affordances would be activated in response to a prime only if this information is relevant for the performance of an action with a target and that this activation would counteract that of functional affordances. We therefore asked our participants to use the target in the same way as if it were the prime and we expected to observe shorter ITs in conditions in which the same common or control tool was presented in the prime and target than in conditions in which different tools were presented. Our results did not support this prediction given that no facilitating effect of compatibility between prime and target was observed on action initiation. Although, the ITs were in general slightly faster when control rather than common tools were used in the prime conditions, the effect of the Prime was not significant.

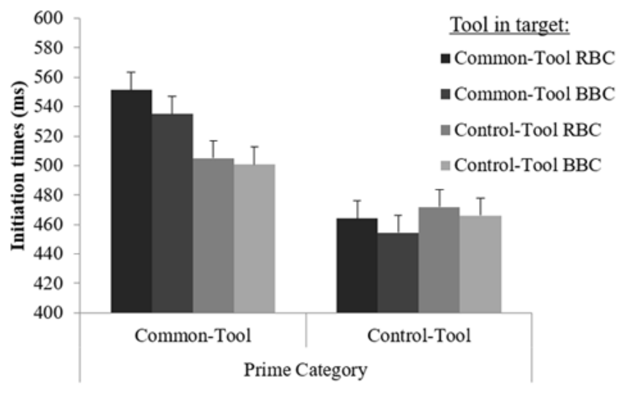

FIGURE 3 | Mean ITs in Experiment 2, as a function of prime category (common tool, control tool) and target (common tool RBC, control tool RBC, common tool BBC, control tool BBC). Error bars represent 95% within-subject confidence intervals.

The second hypothesis was that functional affordances are activated automatically, independently of the situational demand and that they will conflict with situational affordances. We therefore expected to observe longer action ITs in a condition in which a common tool is presented as the prime, and especially when both prime and target are common tools. Our results confirmed our prediction. In fact, longer action ITs were observed when a common tool was presented as the prime, and this finding increased when the target was also a common tool.

Given that in the present experiment the prime indicated the action goal that had to be maintained in working memory until target presentation, there is reason to wonder whether our results might have been influenced by limitations to working memory capacity (Baddeley, 1992, 2003; Vandierendonck, 2016). However, if the processing of irrelevant information is dependent on the resources available in working memory, asking participants to perform an action in the light of the viewed prime should increase the memory load and consequently leave fewer resources available for the processing of functional affordances (Heuer et al., 2016). Thus, the fact that only a low level of resources was available in working memory might have decreased the activation of irrelevant affordances and, consequently, have caused common tool primes to have a less disruptive effect on action initiation (Randerath et al., 2013; Vainio et al., 2014; Grgic et al., 2016). However, our data do not seem to be in agreement with this hypothesis.

GENERAL DISCUSSION

Everyday tools are specific in having a typical function. For example, a glass is typically used to drink from. Sometimes, however, depending on the situation, a tool may be used in an atypical fashion. For instance, we can use a glass to catch a wasp before it becomes a nuisance or, worse still, stings us. In this case, we regard the glass as a trap with the opening at the bottom and no longer as a drinking vessel. The purpose of the present study was to gain a better understanding of the way tools are processed in a context of atypical use, and more precisely during the processing of situational and functional affordances.

In two experiments, participants had to use common tools, which had typical functional affordances, or control tools, which had no such affordances, in combination with boxes involving a new goal (i.e., situational affordances). The way the tools were used with the boxes differed from the typical use of the tools in terms of the end-goal of the action, but not in terms of the grasping and movement gestures. Our main hypothesis was that the conflict between functional and situational affordances should occur if the tool function is automatically activated and that this should be expressed through longer ITs in conditions in which the tool is presented in the prime or target. In general, our results in both experiments confirmed this hypothesis. They therefore suggest that the typical function of a tool may be activated automatically and may consequently disrupt the selection of the relevant action.

It is well known that a tool can activate different affordances (Bub et al., 2008) and that to execute the required action, it is necessary to select the appropriate affordance (Cisek, 2007; Pezzulo and Cisek, 2016). While some studies have focused on conflicts created by the differences in affordances linked not only to the goal but also to the performed gestures – for example the grasp-to-move and grasp-to-use gestures for a calculator are different (Jax and Buxbaum, 2010, 2013; Borghi et al., 2012; Kalénine et al., 2014) –, the present study investigated conflicts created by the differences linked only to the goals, one of which was typical (related to tool function) and the other situational (related to situational demand) and both involving similar gestures. Our results indicate that different gestures are not necessary in order to induce a conflict and that it is sufficient to have different goals. This is consistent with the view that holds that intentions and goals influence visuomotor processes at different levels, from the most abstract plan to more precise parameters (Chemero, 2003; Cisek and Kalaska, 2005; Nonaka, 2013).

To better discuss the extent to which tool function is necessary for action selection in specific situations and the ways in which it may conflict with situational demands, it seems important to specify what the tool function is. Sensorimotor theories suggest that the specific function of a tool is a part of our knowledge about the tool (Buxbaum, 2001; Gallese, 2005; Barsalou, 2008). Such function knowledge is activated automatically irrespective of the situation (Kalénine et al., 2016) and makes it easier to select the typical goal amongst alternative (or atypical) goals (Buxbaum, 2001). Action initiation is simplified if a situational use of a tool is consistent with its typical function. In other cases, the effects of this type of automatic activation are more likely to be disruptive. The effects observed in our study are consistent with the sensorimotor approach. In fact, we observed longer action ITs when common tools were presented as the prime, thus suggesting that functional affordances were activated automatically and somehow entered into conflict with the situational demand. However, and surprisingly, this prejudicial effect on action initiation was not observed when the tool was presented as the target, the processing of which was therefore relevant for the task. It is somewhat difficult to explain these results within the visuomotor framework. The ideomotor approach, which proposes that tool function knowledge is better explained in terms of a framework involving a relationship between the tool and the goal in specific situations (i.e., between a knife and a loaf of bread or between a screwdriver and a screw) (Mizelle and Wheaton, 2010; Osiurak et al., 2010; Baber et al., 2014), seems more appropriate. For Baber et al. (2014), tool use is guided by the goal in response to a specific need and the consequences of this use. It can therefore be suggested that if an action has to be performed using a tool then the situational affordances are predominantly activated and inhibit functional affordances.

Another explanation of our results may be that the activation of functional affordances is related to the gesture that is to be performed rather than to the action goal. In our experiments, functional and situational affordances led to different goals, while the way the tools were grasped and manipulated were very similar. However, the idea that the function of a tool is more closely related to the gesture than to the goal seems somewhat incompatible with studies suggesting that knowledge of tool function can be learned without performing any gestures and instead simply through visualization of the action and its consequences (Jeannerod and Jacob, 2005). This kind of learning is supported by the mirror neurons, which are specific in their ability to process not only sensory and motor information but also the goal of the action (Kohler et al., 2002; Gallese, 2005). The goal of the action can therefore be processed directly and learned without the gesture. It therefore seems that knowledge about the function of a tool is derived from the goal rather than from the gesture (von Hofsten, 2007).

However, it is possible that planning an action activates the processing of relevant motor information, even if the information comes from a stimulus other than the action target (Lindemann et al., 2006). This suggestion is consistent with the view predicting that relevant motor information processing depends on one's intentions and plans (Allport, 1987). Thus, the intention to act in a precise situation could, at a very early stage of information processing, activate a general sensitivity to certain motor components (Massen and Prinz, 2009; van Elk et al., 2010; Przybylski and Króliczak, 2017). In the case of our study, in which grasp and movement were very similar for both functional and situational affordances, activation during processing of the task-relevant motor components in response to the prime might have entered into competition with automatically activated task-irrelevant functional affordances. As we have explained above, the activation of functional affordances when a tool is present in the prime would not be counteracted by the activation of situational affordances, because these would be activated only when an action is required and this was not the case for the primes in Experiment 1. The data from Experiment 2, in which the goal of the action was determined by the prime (the participants were asked to act with the target as if it were the prime they had just seen) are compatible with this explanation, given that longer action ITs were observed in the condition in which a common tool was presented as the prime and were even longer when the target was also a common tool.

To summarize, our study contributes new information to the discussion about the automaticity of the activation of functional affordances. We suggest that this activation might not be fully automatic but might be flexible depending on the situation (Cisek, 2007; Borghi et al., 2012; Borghi and Riggio, 2015; Pezzulo and Cisek, 2016). More precisely, to avoid conflicts between the processing of different types of affordances, the activation of functional affordances may depend on the extent to which a tool is relevant for a task. In this way, no conflict emerges for one and the same tool and the processing of relevant information when an action is initiated may be thought of as adaptive and economical.

AUTHOR CONTRIBUTIONS

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

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Efficiency in Rule- vs. Plan-Based Movements Is Modulated by Action-Mode

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The rule/plan motor cognition (RPMC) paradigm elicits visually indistinguishable motor outputs, resulting from either plan- or rule-based action-selection, using a combination of essentially interchangeable stimuli. Previous implementations of the RPMC paradigm have used pantomimed movements to compare plan- vs. rule-based action-selection. In the present work we attempt to determine the generalizability of previous RPMC findings to real object interaction by use of a grasp-to-rotate task. In the plan task, participants had to use prospective planning to achieve a comfortable post-handle rotation hand posture. The rule task used implementation intentions (if-then rules) leading to the same comfortable end-state. In Experiment A, we compare RPMC performance of 16 healthy participants in pantomime and real object conditions of the experiment, within-subjects. Higher processing efficiency of rule- vs. plan-based action-selection was supported by diffusion model analysis. Results show a significant response-time increase in the pantomime condition compared to the real object condition and a greater response-time advantage of rule-based vs. plan-based actions in the pantomime compared to the real object condition. In Experiment B, 24 healthy participants performed the real object RPMC task in a task switching vs. a blocked condition. Results indicate that plan-based action-selection leads to longer response-times and less efficient information processing than rule-based action-selection in line with previous RPMC findings derived from the pantomime action-mode. Particularly in the task switching mode, responses were faster in the rule compared to the plan task suggesting a modulating influence of cognitive load. Overall, results suggest an advantage of rule-based action-selection over plan-based action-selection; whereby differential mechanisms appear to be involved depending on the action-mode. We propose that cognitive load is a factor that modulates the advantageous effect of implementation intentions in motor cognition on different levels as illustrated by the varying speed advantages and the variation in diffusion parameters per action-mode or condition, respectively.

Keywords: grasping, action planning, implementation intentions, end-state comfort, pantomime, drift diffusion, motor cognition

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1. INTRODUCTION

The development of human interaction with physical tools and objects has come a long way from grasping and using basic stone tools to modern-day video game controllers. Aside from the usage of tools and objects, the grasping movement is a manual skill component for which cognition plays a significant role, as will be detailed below. Considering the multitude of possibilities for grasping an object (variable macroscopic features of grasping include grip force, hand posture, hand shape, and placement on the object), why do we select the grasps that we do?

Healthy individuals pick up a given object with a grip that matches the properties of the object, such as size, weight, and surface texture (Cadoret and Smith, 1996; Flanagan and Wing, 1997; Hermsdörfer et al., 2008; Li et al., 2009). For example, when picking up an iron bar, knowledge of iron's weight characteristics leads to a tight initial grip, as iron is known to be relatively heavy. Grip force can be further mediated by the bar's surface texture, which might be smooth or rough-textured. Smooth textures typically lead to a tighter grip to hinder the object from slipping.

In addition to physical properties, the way we grasp can be influenced by the subsequent action intended for the object (Rosenbaum et al., 1990; Stelmach et al., 1994; Zhang and Rosenbaum, 2008). The phenomenon of adopting an initially uncomfortable hand posture to achieve a biomechanically comfortable end-state is known as the *end-state comfort effect* (see Rosenbaum et al., 2012 for an overview). The effect was examined in several studies using a bar transport task (e.g., Rosenbaum et al., 1990). The task involves a horizontally oriented wooden dowel, raised high enough above a table to allow participants to grasp the dowel with an overhand (pronated/palm-down hand posture) or a more awkward underhand initial grasp (supinated/palm-up hand posture) to subsequently place the dowel onto a target. The studies consistently showed participants using initially awkward hand postures for the sake of a less awkward posture at the end of the transfer task. For example, when participants, planned to place the right end of the dowel onto a target using their right hand, they grasped the dowel with an overhand grasp, but when planning to place the left end of the dowel onto a target (also using the right hand), participants grasped the dowel with a rather uncomfortable underhand grip. In both cases the initially selected grip led to a more comfortable thumb-up (rather than down) end-state when the dowel was placed on the target. Action planning based on end-state comfort is often in effect in activities of daily living. For example, when grasping an object to subsequently use it, we typically apply a certain functional grip. *Functional grasping* describes the act of grasping a tool in a way that allows for its proper use (Creem and Proffitt, 2001; Randerath et al., 2009; Przybylski and Króliczak, 2017). When using a hammer to pound a nail, its handle must be grasped with the thumb pointing toward the hammer's head to allow for proper use. Alternatively, a less functional and biomechanically uncomfortable arm orientation, characterized by extreme joint angles would need to be adopted, to enable goal-directed (but extremely inefficient) use.

The ability to plan, select and execute grasps develops over time. For instance, the proportion of children between the ages of three and five who utilize underhand grips to achieve end-state comfort increases by approximately 25% with each increasing age group (Weigelt and Schack, 2010) and has been shown to increase in children up to the age of nine (Knudsen et al., 2012; Stöckel et al., 2012). However, these cohort effects may be bar rotation specific since planning abilities in other grasping tasks may become apparent at an even earlier age of 5 years (Jovanovic and Schwarzer, 2017; Herbort et al., 2018). It is certain however, that the ability can also be lost. A frequent functional deficiency after left middle cerebral artery stroke is limb apraxia (Buxbaum et al., 2007; Weiss et al., 2008), which affects motor cognition and is typically associated with impaired imitation of gestures or inappropriate pantomiming or actual handling of tools and objects (e.g., Randerath et al., 2011; Buxbaum et al., 2014; Goldenberg and Randerath, 2015; Weiss et al., 2016; Buchmann and Randerath, 2017). When handling tools, not only the use-movement can be affected. Difficulties in forward-planning can also be apparent in the preceding inappropriate non-functional grasping (Randerath et al., 2009, 2010). However, appropriate initial grasping may facilitate the subsequent production of effective object-use.

A helpful compensatory approach for patient populations suffering from impaired plan-based action-selection may be to use alternative routes that are rule-based. Rule-based actions are typically based on stimulus-response associations. We make use of them every day, e.g., when confronted with a red traffic light, we apply the brakes. When the light turns green, we accelerate. In social psychology and motivation science, if-then rules have been found to be effective in the context of *implementation intentions* (Gollwitzer, 1999). They have been shown to reduce cognitive demand by automating stimulus-response associations, thus facilitating goal-directed behavior (for a meta-analysis see Gollwitzer and Sheeran, 2006; for a review see Wieber et al., 2015). A recent meta-analysis demonstrated that if-then planning is also effective in clinical samples of patients with mental health problems (Toli et al., 2016) and recent studies have demonstrated implementation intention effects in physical endurance tasks (Bieleke and Wolff, 2017; Thürmer et al., 2017). Thus for patients with difficulties in forward planning, an alternative could be learning a simple rule that leads to an appropriate functional grasp (e.g., *if* I want to take a hammer, *then* I always grasp it with my thumb pointing toward the head).

To examine the applicability of such an idea to the domain of motor cognition, it is crucial to first systematically investigate the speed and accuracy of rule- compared to plan-based action-selection. One approach to dissociate plan-based from rule-based action-selection, while keeping factors such as stimuli and movement output similar is the rule/plan motor cognition (RPMC) paradigm (Randerath et al., 2013, 2015, 2017). In this paradigm, participants select pronated or supinated grasps and produce manual (object) rotation actions. In the rule-based task, the relationship between stimuli and grip type is fixed by instructed if-then rules. In the plan task, the relationship between stimuli and responses is flexible in that participants make use of a self-selected plan, based on end-state comfort. Results thus far have demonstrated faster reaction times in rule- vs. plan-based grip selection. Randerath et al. (2013) suggested that implementing rule-based grip selection leads to a reduction in cognitive workload, which is in line with the motivation literature on implementation intentions (e.g., Stewart and Payne, 2008; Janczyk et al., 2015). But see McCarty et al. (1999) or Herbort et al. (2017) for a different interpretation of the processing mechanisms underlying the end-state comfort effect.

In motor cognitive tasks, the robustness of these efficiency effects under different conditions remains unclear. For instance, pantomime actions are frequently preferred over real actions for study design because the experimental setting is easier to implement. Accordingly, previous implementations of the paradigm have used either pantomimed rotational movements (Randerath et al., 2015), or pantomimed grasping of familiar tools for which stimuli were presented via two-dimensional pictures (Randerath et al., 2013). Thus far, the applicability of previous (pantomime) results to actual object manipulation has not been tested and cannot be taken as self-evident, since action-mode may modulate efficiency effects. While similar action concepts may be retrieved, differences between modes could occur due to potential deviations in the demands on imagery, perception, on-line visuomotor control, and precision. For example, when grasping an object, pantomimed movements take longer compared to real movements, but object properties such as weight or size are taken into account in both action-modes (e.g., Goodale et al., 1994; Ansuini et al., 2016). For functional tool use, such as scooping soup, the action-modes differ in geometry and kinematics, but correlations of performance measures across the action-modes indicate that individual patterns are stable (Hermsdörfer et al., 2012, 2013). The delivered contextual information differs significantly between action-modes, whereby the level of affordances going along with the required action is manipulated. Compared to pantomime, an actual tool use setting provides fewer degrees of freedom for the required action, which may facilitate the planning process. In line with this, conceptual errors appear to be reduced when patients with tool use apraxia are confronted with a defined tool use setting (Randerath et al., 2011).

Further, accumulated evidence from research with neurological patients (for a review see Goldenberg, 2017) and neuroimaging studies have shown differences between pantomimed and real tool use execution on a neural level. For example, Króliczak et al. (2007) who used functional magnetic resonance imaging to compare the neural mechanisms of pantomimed and real grasping, showed that blood oxygenation level-dependent signal strength significantly differed between real reaching and real grasping, but not between pantomimed reaching and pantomimed grasping.

Here, the main goal was to examine whether the efficiency effects previously found in the RPMC paradigm remain stable across the mode of execution. We propose that compared to end-state comfort based planning, applying an implementation intention based rule expedites action initiation for pantomimed as well as real movements. However, the extent of such efficiency effects may be modulated by the action-mode. The mode producing higher workload (pantomime) is expected to produce relatively stronger efficiency effects. To test this hypothesis, an automated apparatus capable of measuring rotation times and grip orientation was built and applied. It should be noted, that different from typical end-state comfort tasks as described above, we explicitly instructed participants to grasp in a comfortable way.

As we are particularly interested in the information processing component of reaction times (grip selection), which can be masked by differences in speed-accuracy trade-off, speed of motor-response encoding and other processes occurring between stimulus presentation and response, we ran a simulation study to show the suitability of our collected reaction time data for drift diffusion modeling (DDM; Voss et al., 2013, 2015), and describe the effects of our experimental manipulations on the correct selection of pronated or supinated grip postures in terms of diffusion model parameters. The Ratcliff diffusion model (Ratcliff, 1978; Ratcliff and McKoon, 2008) represents the decision process as a Wiener process originating from a starting point (z) located between two decision boundaries (commonly an upper boundary a and a lower boundary 0). A decision is made when one of the two decision boundaries is reached. In other words, decisions are modeled as noisy stochastic processes that drift toward decision boundaries as information accumulates. In binary decision tasks (i.e., selection of pronated vs. supinated posture) the diffusion model allows for the statistical decomposition of reaction times into parameters reflecting (among others) the rate of information accumulation (drift rate, v), distance between decision thresholds (boundary separation, a), and duration of non-decision components (e.g., stimulus encoding, preparation of motor response, task switching, visualization) combined in the non-decision time parameter t_0 or T_{er} (Voss et al., 2004). In a diffusion model with an unbiased starting point, the reaction time difference between a given relatively slower decision (hypothetically in the plan-based task) and a relatively faster decision (hypothetically in the rule-based task) can be accounted for by differences in a, v, t_0 or a combination of those parameters. Lower a indicates that less information is required for a decision to be made, leading to faster reaction times and a higher error probability (more liberal response criterion). Lower v implies less efficient processing of information. Differences in t_0 between conditions indicate that processes not directly involved in the decision differ (see **Figure 1**).

In *Experiment A* we directly compare pantomime and real object implementations of the RPMC paradigm in a within-subjects design. Similar to previous results in studies applying the RPMC paradigm with pantomimed actions (Randerath et al., 2013, 2015, 2017), we predict that reaction times will be faster in rule trials than in plan trials. We expect the drift parameter v to be larger in the rule task, as the strengthening of the stimulus-action link suggested by the implementation intention literature should increase the efficiency of information uptake. Furthermore, we expect faster reaction times for the more typical overhand grasp than for underhand grasps, and equally fast reaction times for the dominant and non-dominant hands, in line with previous research by Randerath et al. (2013).

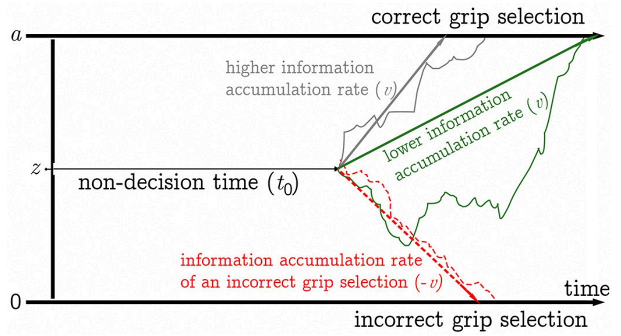

FIGURE 1 | Schematic illustration of the diffusion model. Non-decision time components are combined in the t_0 parameter (represented by the thin black arrow). Three decision processes are shown (solid paths lead to correct grip selection, dashed path leads to incorrect grip selection). The decision processes start between the two decision boundaries (at 0 and a) at the level of the starting point z. A grip is selected when the corresponding decision boundary is reached. The gray path shows a decision process with a relatively higher mean rate of information accumulation (high drift rate (v), represented by the gray arrow), the green path shows a decision process with a lower mean rate of information accumulation (lower v, represented by the green arrow). The red path shows a decision process leading to an incorrect grip selection, the red arrow represents the corresponding rate of information accumulation.

As the pantomime condition places greater demand on mental imagery, this increase in cognitive workload is proposed to increase t_0. Furthermore, we hypothesize that relative differences in reaction times between rule and plan tasks will be larger in the pantomime-movement condition compared to the real object condition, as rule-based action-selection should allow greater allocation of cognitive resources toward the more demanding motor imagery processes involved in the pantomime condition.

In *Experiment B* we investigate the effects of task switching in the real object manipulation action-mode by comparing two versions of the experiment, within-subjects. In the mixed version, rule- and plan-based actions were presented in a pseudo-randomly mixed sequence, while the blocked version consisted of a rule-task-only and a plan-task-only block. As in Experiment A, we predict that reaction times will be faster in rule trials than in plan trials and expect the rate of information uptake, v, to be larger in the rule task than in the plan task. Also as in Experiment A, we expect faster reaction times for the more typical overhand grasp than for underhand grasps, and equally fast reaction times for the dominant and non-dominant hands. In the mixed condition, prolonged reaction times compared to the blocked condition are predicted because of increased cognitive load attributable to task switching costs (Monsell, 2003). As such, we expect t_0 to be higher in the mixed condition than in the blocked condition (Schmitz and Voss, 2012, 2014). As the presentation of trials in task-pure compared to mixed fashion should lead to an increase in task readiness, we expect a higher drift rate v in the blocked condition compared to the mixed condition (Schmitz and Voss, 2012, 2014).

Moreover, the experiments aim to elucidate the extent of the similarity of motor outputs elicited by either plan- or rule-based action planning by measuring the duration of handle rotations. Thus far, there has been no attempt to extract the rotation component in the context of the RPMC paradigm.

To summarize, the aim of this work is to examine the behavioral stability of efficiency effects in the RPMC paradigm in different action-modes and under conditions of varying cognitive load. To complement typical RT analyses (ANOVA), we applied diffusion modeling as it seems to be a suitable approach for the analysis of action selection processes within the present paradigm.

2. EXPERIMENT A

2.1. Methods

Experiments A and B were approved by the ethics committee of the University of Konstanz. All participants gave written informed consent in accordance with the Declaration of Helsinki.

2.1.1. Participants

Based on the task means reported in Randerath et al. (2015; Experiment 3 ($N = 21$); condition averages, Plan: $M = 966.5$ ms, $SD = 154.4$ ms, Rule: $M = 801.2$ ms, $SD = 96.1$) we calculated a minimum sample size of $N = 8$ (with $\alpha = 0.05$, $power = 0.8$) using G*Power 3 (Faul et al., 2007), to detect task differences in pantomime condition RTs. For this experiment we included a sample of 16 healthy participants, since we hypothesized that task effects would be reduced in the real action-mode. The sample consisted of 12 female and 4 male participants with a mean age of 25.4 years ($SD = 4.7$ years). All participants had either recently received or were currently pursuing a university degree. Handedness was assessed using the Edinburgh Handedness Inventory version by Salmaso and Longoni (1985). One participant was left-hand dominant; all other participants were right-hand dominant. Participants received either study-credits or 20 EUR for their participation and were assigned to one of four conditions to counterbalance the order of real and pantomime sessions and task-cue color assignment (see next section). The assignment was matched for age. Instructions were given in German. The experimenter confirmed language fluency. Participants had normal or corrected-to-normal vision.

2.1.2. Materials and Procedure

Each participant was tested in two 45–60 min sessions, namely, a real object session and a pantomime session. These sessions were no more than 3 days apart. All participants gave written consent to both participation and video recording of the experimental sessions.

The experiment was presented with SuperLab 5 (Cedrus Corporation, San Pedro, CA, USA) on a 24-inch screen at a resolution of 1,920 × 1,080 pixels, run from on-board graphics of an Intel Core i7 4790 @3.6 GHz CPU with 16GB of RAM running a 64-bit version of Windows 8.1.

The experimental setup (see **Figure 2**) was adjusted to place the center of the screen's viewable area at participants' eye level, with chair height adjusted to put participants' thighs and shins at a 90° angle with feet flat on the floor. This was accomplished by placing the experimental setup on a height-adjustable table, which allowed the distances between the monitor, RPMC

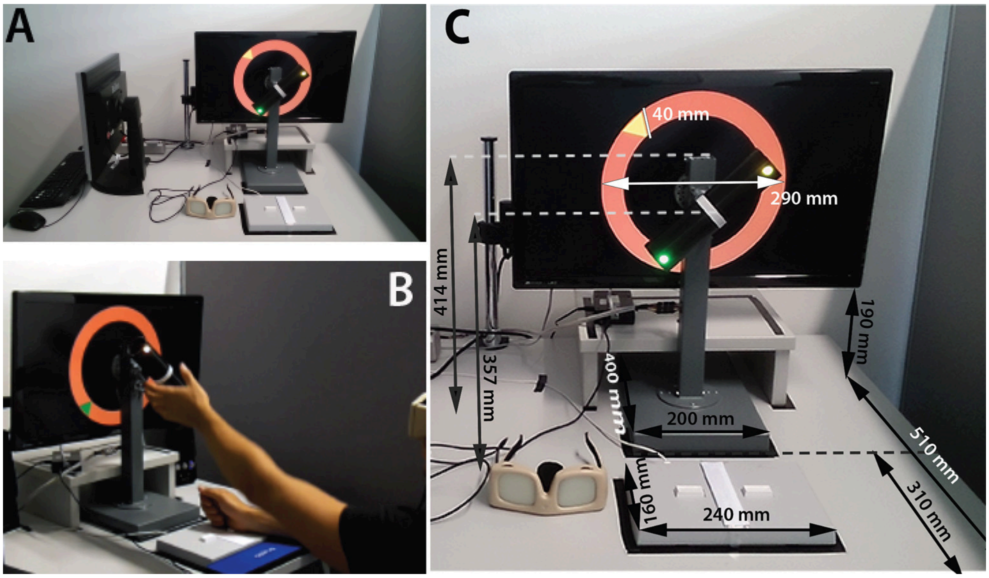

FIGURE 2 | (A) shows the experimental setup (without speakers) with the monitor showing an underhand trial for the right hand. The visual occlusion goggles in their closed state are located to the left of the two-button response pad. The experimenter monitor with keyboard and mouse, used to input participant data, on-line grip error coding, and general experiment control can be seen on the left of the image. **(B)** shows a participant executing an underhand grasp with the left hand, while using the inactive right hand to keep the right response button pressed as instructed. **(C)** shows dimensions of the equipment used and distances between the equipment. Arrows leaving the picture plane extend to the forward edge of the table (80 mm from the forward edge of the response pad). Distance vectors parallel to the table plane are parallel and perpendicular to respective table edges. Vertical distance vectors are orthogonal to the table plane.

apparatus (see Figure S1 for details), and response pad to be kept identical for all participants while keeping viewing angles constant (see **Figure 2C**).

Participants wore Translucent Technologies PLATO visual occlusion goggles (http://www.translucent.ca), which hid the monitor and apparatus from view before each trial. Participants were instructed to keep both buttons of the response pad (Lumina RB-540, Cedrus corporation) pressed with a loosely balled fist (thumbs away from the response buttons, 5th fingers toward the response buttons) while the goggles were "shut" (lenses switched to their opaque state). Before each trial, a voice recording (1,000 ms duration) saying either "left hand" or "right hand" instructed participant which hand to use for the upcoming trial. The recording was followed by a variable inter-stimulus-interval (500, 800, or 1,100 ms). As soon as the goggles "opened" (lenses switched to their transparent state) participants had to release the respective response button, perform the handle rotation task, and then return the hand to the response button, which triggered opacity of the lenses before the next trial (see **Figures 2A,C**). Reaction times were measured as the interval between the opening of the goggles and button release. Movement times measured the interval between button release and button press.

The implementation of the RPMC paradigm used in Experiments A and B consisted of 128 trials (8 × 16 trial types) per session. The 16 trial types were based on: 2 tasks (plan vs. rule) × 2 grips (overhand vs. underhand) × 2 hands (left vs. right) × 2 colors of the target (i.e., green or yellow vs. blue or magenta). Light emitting diodes (LEDs) on the ends of the apparatus handle (**Figure 2**) specified the task (rule or plan). LED color combinations (e.g., Plan: green/yellow, Rule: blue/magenta) were counterbalanced between participants. Trials further varied with respect to LED color placement (i.e., green on the right or left side of the handle etc.) and on-screen location of the target (upper vs. lower and right vs. left quadrant of the on-screen circle), see **Figure 2**. Initial handle angles (from the participant perspective) were 45° for the right hand and 315° for the left hand, relative to the vertical (0° or "12 o'clock") position (see **Figure 2A**). Those angles were selected because previous research by Johnson (2000) has shown hand orientations of those angles to be rated as equally comfortable. Successful handle rotation always spanned an angle of 90°.

The 128 trials per session were divided into four blocks of 32 trials. In each of the four blocks the 16 trial types were presented twice. Trials in each block were presented in pseudo-randomized order, such that there would not be more than three consecutive trials which utilized the same hand, task, or grip.

Participants were instructed to rotate the handle in a way that would align the colored arrow (40 mm equilateral triangle) with the light on the handle of the same color as the arrow and that the apparatus would block further rotation when they had rotated the handle far enough. Participants were further instructed to execute each rotation as comfortably as possible and that this meant that hand posture before and after the rotation should be comfortable and natural. Participants were shown an example of a comfortable or an uncomfortable end position. This instruction was given independently of task. They were further told that the middle finger should remain in contact with a white strip of tape affixed to the center of the handle, which spanned the visible length of the handle's equator. It was also emphasized, that thumb and index fingers should be on the same side of the white strip, regardless of hand posture. It was then explained that the white strip divided the handle into two sides, meaning the "green side" was the side on which the green light was, and the "yellow side" was the side on which the yellow light was and so on. Participants were explicitly told to rotate the handle in the direction that constituted the shortest distance.

Participants were then informed that they would be completing two different tasks, referred to as the green/yellow and the pink/blue (most participants referred to magenta as "pink") tasks. For half of the participants the green/yellow task was the plan task; for the other half, it was the rule task. For the sake of simplicity, the following task description will assume a participant for whom green/yellow coded for the rule task, and pink/blue coded for the plan:

In the plan task participants were instructed to rotate the pink light to align with the pink arrow or the blue light to align with the blue arrow. To do so, participants were asked to form the intention to execute the movement as comfortably as possible. They were then presented with a cardboard sheet showing two rectangles of pink and blue color, with a text stating "*I will execute the movement as comfortably as possible.*" printed on it, and were asked to read the statement out loud.

For the rule task, participants were told to grasp the handle such that their thumb would be on the same side of the handle as the light of the same color as the arrow stimulus. That instruction was repeated once before participants were instructed to form the following implementation intentions: "*If the arrow is green, then I will place my thumb on the green side of the handle*" and "*If the arrow is yellow, then I will place my thumb on the yellow side of the handle*." Participants were then shown another piece of cardboard, this time showing green and yellow rectangles, displaying the text of the intentions they were asked to form for the rule task. Participants then read the printed text out loud. They then completed 16 practice trials (which included all stimulus/handle combinations). Both pieces of cardboard remained visible to participants to the left and right of the PC monitor for the duration of the 16 RPMC training trials.

Participants were tested in two sessions. In Experiment A half of the participants received the pantomime version of the RPMC experiment in the first session, while the other half received the real object version first. Color combinations indicating plan or rule trials were kept constant across sessions for each participant. Prior to the start of the RPMC paradigm participants were instructed to perform the task as quickly as possible but with an emphasis on accurate task performance.

2.1.3. Data Analysis

Dependent variables in the RPMC paradigm were reaction time (RT, time from opened goggles to button release), movement time (MT, time between button release and button press), and errors. Additionally, handle rotation time (rotTime) was measured by the apparatus. For technical reasons (see supplement) measurement of rotation time began as soon as the handle deviated greater than 3.125° from the start position in the proper direction of rotation (remaining span of handle rotation at $T_0 = 86.875^\circ$).

For each participant, the data were stratified by combinations of action-mode (real or pantomime), task (rule or plan), grip (pronated or supinated) and hand (non-dominant or dominant). Trials containing erroneous participant responses in the RPMC task were identified from records of on-line participant observation and confirmed by review of recorded video material. Errors were coded when participants utilized either the wrong hand or grip type (which would lead to an uncomfortable end position), rotated the handle in the wrong direction, or removed their hand from the response pad before the PLATO goggles opened. These trials were removed from the data set prior to outlier screening. Error trials, as well as trials containing time measure outliers, were excluded from the analysis of reaction and movement times. The Generalized Extreme Studentized Deviate (ESD) test for multiple outliers (Rosner, 1983) was used to detect outliers. Normality of time-measure residuals was assessed by reviewing normal probability plots and with the Kolmogorov-Smirnov test which indicated that RT, MT, and rotation time residuals were approximately normally distributed, $p > 0.15$.

We calculated three repeated measures analyses of variance (ANOVA) using Statistica Version 13 (http://software.dell.com); one for each of the dependent variables RT, MT, and rotation time. Based on our hypotheses, each ANOVA was constrained to the main effects of task (rule/plan), grip (pronated/supinated), hand (non-dominant/dominant), and action-mode (pantomime/real) as well as the task*mode interaction. We calculated t-contrasts comparing tasks in each action-mode to test our RT hypothesis. To correct for family-wise error rate, we adjusted p-values using the Holm-Bonferroni procedure. Significant interactions in variables other than RT were analyzed with Bonferroni *post-hoc* tests, since we only formulated a priori hypotheses for RTs.

For the analysis of grip-error data, we used non-parametric tests as the data were not normally distributed (Kolmogorov-Smirnov test: $p < 0.05$). The number of grip errors (utilizing pronated grips in trials requiring a supinated grip and vice versa) was compared using the Wilcoxon-Test for paired samples in four sets of comparisons (Plan vs. Rule trials, Overhand vs. Underhand trials, Dominant vs. Non-dominant hand trials, Real vs. Pantomime trials) at a Bonferroni corrected α level of $\alpha_{\text{bf}} = 0.0125$ to account for multiple comparisons.

2.1.3.1. Diffusion model analysis and simulation study

Diffusion model parameters were estimated using the fast-dm-30.2 program (Voss and Voss, 2007, 2008; Voss et al., 2015). Accuracy-coded data-sets for diffusion model analysis were created for each participant by adding the previously removed grip-errors to the outlier free data sets. Additionally, an upper cut-off of 1800 ms and a lower cut-off of 200 ms was applied to error RTs. At the lower cut-off, on average, correctness of grip selection was approximately at chance-level (Ratcliff and McKoon, 2008). Following the recommendation of Ratcliff and Tuerlinckx (2002) the upper cut-off was set so that 0.5% of responses were slower than the upper cut-off. The parameters

v, t_0, and a were allowed to vary by all possible combinations of action-mode and task, but not grip and hand to increase the number of trials in each factor combination and thus improve the reliability of parameter estimates. The parameter d, which represents the difference in the speed of response execution between correct and incorrect responses was allowed to vary by participant. To counteract the negative effect of possible fast contaminant RTs, the inter-trial non-decision time variability parameter st_0 was added and allowed to vary in the same way as v, t_0, and a (Lerche and Voss, 2016). Since the data were accuracy coded, the starting point z was fixed to 0.5 (no response bias). All other parameters were fixed to 0. Given the relatively low number of trials, Maximum-Likelihood was chosen as the optimization criterion. For further details see Voss et al. (2015).

To confirm that the RPMC paradigm is apt for diffusion modeling we ran a simulation study following the recommendations in Voss et al. (2015). In each experiment, 5,000 data sets per participant were simulated by first creating multivariate normal distributions defined by the covariance matrix of empirical parameter estimates (MATLAB script can be downloaded from https://github.com/MoCogKonstanz/RPMC) from which simulated parameter estimates were drawn. The simulated parameter estimates were then split by condition and participant. Subsequently, the *construct-samples* tool included in fast-dm was used to create 5,000 data sets for each participant in each of the four factor combinations with 64 trials each. These condition-specific data sets were then merged into 5,000 complete data sets per participant. In turn, the 5,000 complete data sets were entered into diffusion model analysis using the same settings as for the analysis of empirical data. For each simulated data set, the 95th percentile of fit indices was calculated. Following the recommendations of Voss et al. (2015), all empirical data sets fitting worse than 5% of the worst fitting corresponding simulated data sets (>95th percentile) would have been excluded from diffusion model analysis, as fits worse than the 5% criterion would have indicated that those data sets are not suitable for diffusion modeling. As all empirical data sets fit the diffusion model better than the 5% criterion suggested by Voss et al. (2015), we conclude that the paradigm is suitable for diffusion modeling. Fit indices for Experiment A and Experiment B data sets are shown in Table S1.

2.2. Results Experiment A

2.2.1. Reaction Time

The ANOVA of RTs showed a significant main effect of action-mode, with slower mean RTs in the pantomime session of the experiment than in the real object session. There was also a main effect of task, with participants showing slower mean RTs in the plan task than in the rule task. There was a significant interaction between task and action-mode (see **Figure 5**). The planned comparisons showed that rule RTs were significantly faster than plan RTs in the pantomime action-mode, $t_{(15)} = 3.32$, $p = 0.005$, but not in the real action-mode, $t_{(15)} = 1.27$, $p = 0.224$. There were no significant main effects of grip or hand on RTs. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Main effects are shown in **Figure 3**. Full factorial data are given in Tables S2, S3.

2.2.1.1. Diffusion parameters

Action-mode had a significant effect on t_0 with significantly longer non-decision times in the pantomime action-mode than in the real action-mode. Task had a significant main effect on

TABLE 1 | Main effect means and standard deviations.

Experiment	Factor	Level	RT		MT		rotTime	
			M	*SD*	*M*	*SD*	*M*	*SD*
Exp. A	Mode	Pantomime	772.6	170.9	1951.5	632.1		
		Real	583.8	135.6	1982.6	543.6		
	Task	Plan	703.4	159.3	1991.6	569.5	436.1	173.0
		Rule	653.0	126.4	1942.6	571.8	426.9	176.9
	Grip	OH	672.5	130.5	1901.1	533.2	390.3	176.5
		UH	683.8	150.6	2033.0	611.0	472.6	177.8
	Hand	ND	684.7	143.6	2016.9	583.0	441.5	185.3
		Dom	671.7	138.5	1917.3	561.4	421.4	168.1
Exp. B	Condition	Blocked	620.8	100.0	1701.9	234.7	349.4	66.7
		Mixed	712.8	142.3	1798.8	300.1	339.7	96.5
	Task	Plan	691.2	118.8	1773.7	222.4	345.5	77.3
		Rule	642.4	112.6	1727.1	255.5	343.6	76.4
	Grip	OH	654.5	103.6	1656.7	231.7	310.7	72.1
		UH	679.1	125.5	1844.1	240.7	378.3	78.0
	Hand	ND	670.4	112.9	1767.0	229.2	337.5	76.4
		Dom	663.2	116.1	1733.7	237.1	351.6	75.0

The table gives means (M) and standard deviations (SD) of Experiment A and Experiment B main effect reaction times (RT), movement times (MT), and rotation times (rotTime) in milliseconds. ND, non-dominant hand; Dom, dominant hand; OH, overhand grip; UH, underhand grip.

TABLE 2 | Interaction means and standard deviations.

Experiment	Session	Task	RT		MT		rotTime	
			M	*SD*	*M*	*SD*	*M*	*SD*
Exp. A	Pantomime	Plan	816.3	210.7	1988.3	618.8		
		Rule	728.8	140.0	1914.8	648.7		
	Real	Plan	590.4	136.3	1994.8	555.8	436.1	173.0
		Rule	577.1	138.1	1970.4	534.1	426.9	176.9
Exp. B	Blocked	Plan	642.5	132.5	1701.4	307.1	345.3	93.9
		Rule	599.1	127.0	1702.5	300.0	353.5	86.1
	Mixed	Plan	739.8	187.9	1846.0	351.1	345.7	115.7
		Rule	685.7	165.6	1751.6	395.3	333.6	117.9

The table gives means (M) and standard deviations (SD) of Experiment A and Experiment B interaction effect reaction time (RT), movement time (MT), and rotation time (rotTime) data in milliseconds.

TABLE 3 | Experiment A and B ANOVA results.

Experiment	Effect	RT				MT				rotTime			
		$F_{(1,15)}$	p	p_{adj}	η_p^2	$F_{(1,15)}$	p	p_{adj}	η_p^2	$F_{(1,15)}$	p	p_{adj}	η_p^2
Exp. A	Intercept	375.27	0.000		0.96	190.47	0.000		0.93	98.05	0.000		0.87
	Mode	33.99	0.000	0.000***	0.69	0.17	0.684	–	0.01				
	Task	9.51	0.008	0.023*	0.39	16.60	0.001	0.004**	0.53	1.39	0.257	–	0.08
	Grip	2.09	0.169	–	0.12	18.57	0.001	0.003**	0.55	27.41	0.000	0.000***	0.65
	Hand	2.35	0.146	0.293	0.14	16.05	0.001	0.003**	0.52	1.77	0.203	0.406	0.11
	Mode*Task	10.12	0.006	0.025*	0.40	1.80	0.200	0.400	0.11				
		$F_{(1,23)}$	p	p_{adj}	η_p^2	$F_{(1,23)}$	p	p_{adj}	η_p^2	$F_{(1,22)}$	p	p_{adj}	η_p^2
Exp. B	Intercept	549.71	0.000		0.96	910.48	0.000		0.98	347.86	0.000		0.94
	Condition	15.52	0.001	0.003**	0.40	2.00	0.170	–	0.08	0.27	0.609	–	0.02
	Task	20.77	0.000	0.001***	0.47	2.47	0.130	–	0.10	0.03	0.858	–	0.01
	Grip	8.26	0.009	0.026*	0.26	71.42	0.000	0.000***	0.76	99.42	0.000	0.000***	0.83
	Hand	1.15	0.295	–	0.05	8.39	0.008	0.033*	0.27	2.98	0.099	–	0.14
	Condition*Task	0.24	0.632	–	0.01	7.55	0.011	0.034*	0.25	1.71	0.204	–	0.04

*The table gives effect sizes and significance of Experiment A and B repeated measures ANOVAs. Effects with Holm-Bonferroni adjusted p-values $p_{adj} < 0.05$ are marked *, with $p_{adj} < 0.01$ are marked **, with $p_{adj} < 0.001$ are marked***. Effect sizes are reported as partial eta squared (η_p^2) values. RT, reaction time; MT, movement time; rotTime, rotation time.*

drift rate, with significantly higher v in the rule task compared to the plan task. The mode*task interaction of drift rate did not survive family-wise error correction. The main-effect of Task on boundary separation (a) was not significant after family-wise error correction. The significant mode*task interaction showed significantly lower a for the plan task compared to rule task only in the pantomime action-mode, $p = 0.006$. See **Table 5** for DDM ANOVA results and **Table 4** for DDM means and standard deviations. See **Figure 6** for mode*task interaction plots of diffusion model parameters.

2.2.2. Movement Time

The ANOVA revealed a significant main effect of task on MTs, with faster MTs in the rule task than in the plan task. The significant effects of grip type showed faster MTs in overhand trials than in underhand trials. Dominant hand MTs were significantly faster than non-dominant hand movement times. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Main effects are shown in **Figure 3**. Full factorial data are given in Tables S2, S3.

2.2.3. Rotation Time

There was a significant main effect of grip on rotation times, with overhand grips producing faster rotation times than underhand grips. As rotation times were measured with the apparatus, the result applies only to the real object mode session. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Main effects are shown in **Figure 3**. Full factorial data are given in Tables S2, S3.

2.2.4. Grip Errors

There were a total of 77 grip errors in 4096 trials. The mean error rate was 1.88%. There were 2048 trials in the plan task as well as in the rule task. In the plan task, 62 errors (3.027%)

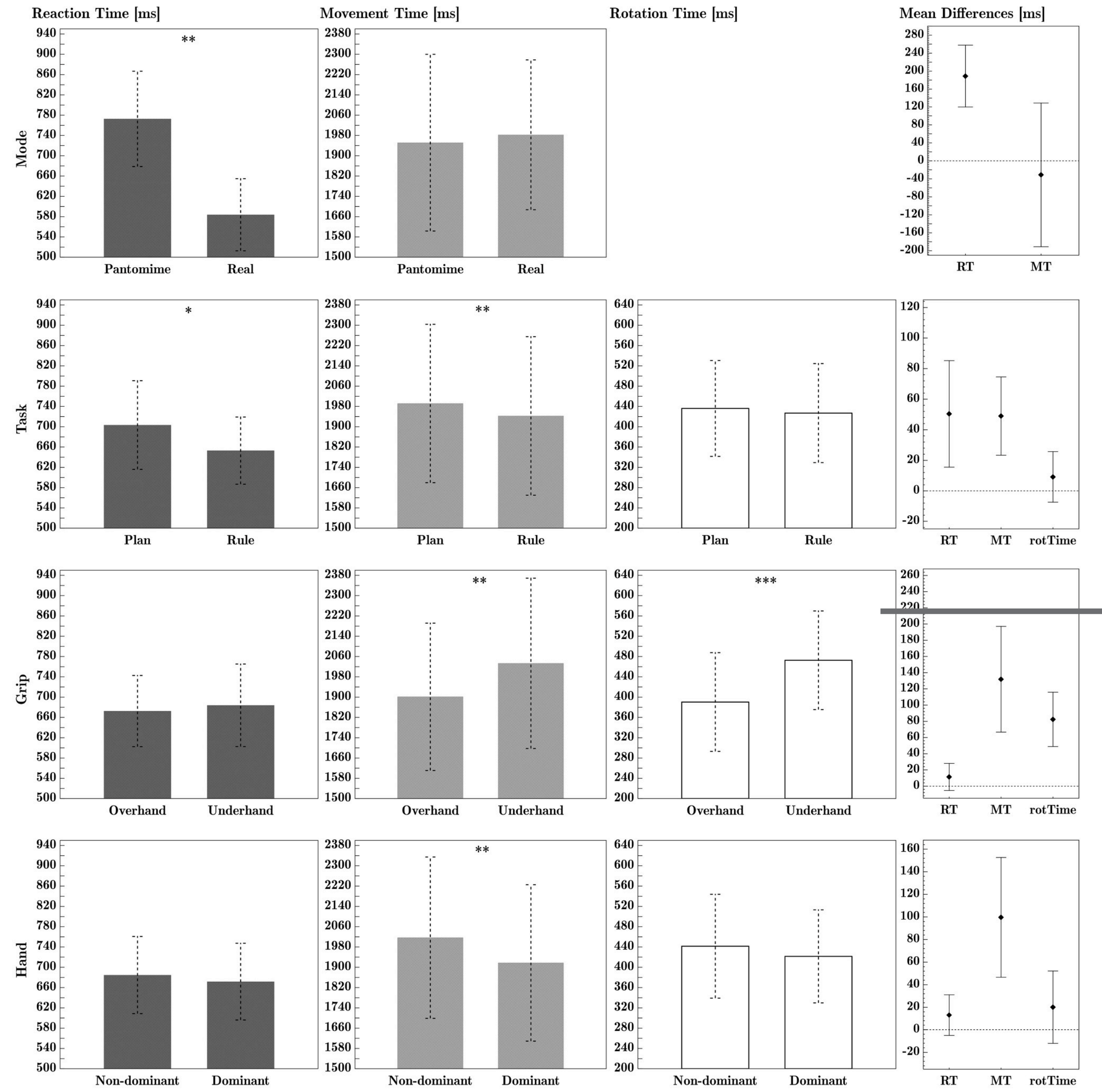

FIGURE 3 | Experiment A ANOVA main effects, for (from left to right column) reaction time, movement time and rotation time. Within-factor differences are shown in the far right column. All times are given in milliseconds. Error bars represent 95% confidence intervals. *, **, and *** denote significant differences with Holm-Bonferroni adjusted *p*-values $p_{adj} < 0.05$, < 0.01, and < 0.001, respectively. Calculation of mean difference times: Mode difference = (Pantomime − Real); Task difference = (Plan − Rule); Grip difference = (Underhand − Overhand); Hand difference = (Non-dominant − Dominant). See **Table 3** for effect sizes and *p*-values.

were observed, and in the rule task, 15 errors (0.732%) were observed. Moreover, of 2048 trials in the pantomimed-movement condition, 45 (2.197%) produced erroneous hand postures. In the real-movement condition, 32 errors (1.562%) were observed in 2048 trials. Pair-wise Wilcoxon comparisons of task showed that the number of grip errors significantly differed only in the plan, $M = 3.88$, $SD = 3.24$, vs. rule, $M = 0.94$, $SD = 1.61$, comparison , $W(13) = 4.0$, $Z = 2.90$, $p = 0.004$. The real, $M = 2.00$, $SD = 1.93$, vs. pantomime, $M = 2.81$, $SD = 2.90$, error comparison was not significant with, $W(11) = 24.5$, $Z = 0.76$, $p = 0.45$.

2.3. Discussion Experiment A

In this experiment, the same actions could be achieved with either rule-based or plan-based instructions. In contrast to plan-based actions our rule-based actions were guided by implementation intentions (if-then rules), and as expected we found faster processing for this task compared to when prospective planning was involved. Our major point of interest was how action-mode modulates this processing advantage. We found that efficiency effects are stronger in the pantomime mode vs. when using the real object. Further, timing across the movement stages was affected differently by the assessed variables. Effect sizes (η_p^2) indicate that the movement initiation phase (RT) seems to be predominantly influenced by action-mode and task, while the time for hand transport (MT) is still modulated by task but also by grip type as well as the used hand. Rotation time appeared to be predominantly influenced by grip type.

2.3.1. Task and Action-Mode Effects

As hypothesized, rule task RTs were shorter than plan task RTs, particularly in the pantomime mode. The larger advantage of rule-based action-selection over plan-based action-selection in the pantomime compared to the real action-mode is illustrated by the significant interaction between task and action-mode (see **Figure 5**). Although we measured a slight advantage of rule RTs over plan RTs in the real object condition (on average 13.3 ms), this tendency was not statistically significant. Interestingly, MTs were affected by task similarly to RTs (see **Figure 5**). It is possible that a portion of the grip selection process carried over into the movement phase (measured by MTs) and thus reduced the task difference in the planning phase (measured by RTs). This likely affected the real action-mode proportionally stronger due to the smaller magnitude of the task difference.

As expected, drift rates appeared to be sensitive to task, with participants showing significantly higher drift rates (v) in the rule task than in the plan task. This confirms that the rule advantage, judging by effect sizes given in **Table 5**, primarily stems from an optimized grip-selection process, rather than optimization of decision boundaries or non-decision components. With regard to grip errors, the analyses show significantly more errors in the plan task than in the rule task. Though more grip errors were made in the pantomime-movement condition than in the real-movement condition, the difference between action-modes was not significant. However, in the pantomime condition, the diffusion model showed that participants adopted significantly wider decision boundaries (larger a) in the rule task than in the

TABLE 4 | Experiment A and B diffusion model means and standard deviations.

Experiment	Condition	Task	Mean v	SD v	Mean t_0	SD t_0	Mean a	SD a
Exp. A	Pantomime	Plan	3.09	1.26	0.580	0.149	1.41	0.59
		Rule	5.93	2.63	0.515	0.162	2.36	0.97
	Real	Plan	4.73	2.11	0.427	0.137	1.49	0.64
		Rule	5.65	2.57	0.433	0.142	1.50	0.79
Exp. B	Blocked	Plan	4.43	1.77	0.485	0.10	1.70	0.93
		Rule	6.19	2.16	0.430	0.13	2.39	1.31
	Mixed	Plan	3.62	2.40	0.517	0.14	1.93	1.53
		Rule	4.56	2.30	0.492	0.15	2.14	1.53

The table gives means and standard deviations of Experiment A and B drift parameters. t_0 is given in seconds. v, drift rate; t_0, non-decision time; a, boundary separation.

TABLE 5 | Experiment A and B diffusion model parameter ANOVA results.

Experiment	Effect	v				t_0				a			
		$F_{(1,15)}$	p	p_{adj}	η_p^2	$F_{(1,15)}$	p	p_{adj}	η_p^2	$F_{(1,15)}$	p	p_{adj}	η_p^2
Exp. A	Intercept	180.18	0.000		0.92	222.96	0.000		0.94	316.88	0.000		0.96
	Mode	1.44	0.249	–	0.09	30.97	0.000	0.000***	0.67	3.47	0.082	–	0.44
	Task	18.27	0.001	0.002**	0.55	3.29	0.090	0.179	0.18	6.09	0.026	0.052	0.09
	Mode*Task	4.85	0.044	0.087	0.24	2.54	0.132	–	0.14	8.08	0.012	0.037*	0.24
		$F_{(1,23)}$	p	p_{adj}	η_p^2	$F_{(1,23)}$	p	p_{adj}	η_p^2	$F_{(1,23)}$	p	p_{adj}	η_p^2
Exp. B	Intercept	254.18	0.000		0.92	535.51	0.000		0.96	190.12	0.000		0.96
	Condition	11.24	0.003	0.008**	0.33	4.84	0.038	0.114	0.17	0.00	0.978	–	0.16
	Task	9.37	0.006	0.011*	0.29	4.17	0.053	–	0.15	2.38	0.136	0.273	0.05
	Cond*Task	1.48	0.235	0.235	0.06	0.59	0.450	–	0.03	0.74	0.400	–	0.14

*The table gives effect size and significance for Experiment A and B repeated measures ANOVAs of the drift parameters v, t_0, and a. Effects with Holm-Bonferroni adjusted p-values p_{adj} < 0.05 are marked *, with p_{adj} < 0.01 are marked **, with p_{adj} < 0.001 are marked ***. Effect sizes are reported as partial eta squared (η_p^2) values. v, drift rate; t_0, non-decision time; a, boundary separation.*

plan task, indicating more cautious responding. It appears that the higher rates of information accumulation in the rule task are able to offset this boundary separation induced latency, as RTs in the pantomime action-mode were significantly faster in the rule task than in the plan task. Finally, the prolonged non-decision time (t_0) in the pantomime condition compared to the real condition suggests that differences in non-decision times (t_0 parameter) between action-modes may be good approximations of the time required for movement imagery.

2.3.2. Effects of Hand and Grip Type

We found a dominant hand advantage for MTs. One likely explanation is that grasping movements are usually performed with the dominant hand and are thus more trained. Overhand grasps produced significantly shorter MTs and rotation times than underhand grasps. Similar to the dominant hand advantage in MTs, we interpret the overhand advantage in terms of training by way of more frequent use. We speculate that biomechanical constraints may have contributed to the longer rotation times in underhand grasps. Although the handle angles we used have previously been rated as equally comfortable for pronated and supinated hand postures, it is possible that overhand grips (during initial grasping, thumbs were pointed inward and down) induced more muscle tension in the forearm during initial grasping, which could have led to faster handle rotations.

2.3.3. Experiment A Conclusion

Succinctly, the planning phase seems to be predominantly influenced by action-mode and task. This resulted in slower responses in the pantomime condition compared to the real condition, and in line with the findings reported by Randerath et al. (2013, 2015, 2017), this also resulted in faster responses during rule-based action initiation compared to plan-based initiation. The execution phase appears to be modulated by hand, grip type, and task. Participants demonstrated faster movements when solving tasks in the real vs. the pantomime condition, quicker execution of overhand compared to underhand grasping movements, and faster movements in rule compared to plan trials. As hypothesized and previously reported by Randerath et al. (2013), there was no significant difference between dominant and non-dominant hands in the planning phase. However, in the movement phase, dominant hand movements were significantly faster than non-dominant hand movements. Contrary to our hypothesis and the findings of Randerath et al. (2013), we did not find a significant RT difference as a function of grip posture, in the planning phase. The extracted rotation-movement however, appears to be predominantly influenced by grip type, with overhand rotations being faster than underhand rotations. Here, task does not appear to have an effect.

To conclude, time measures of movement planning and movement execution are susceptible to efficiency effects, with quicker responses for parameters inducing less cognitive load or higher familiarity. Whether the effect of grip type on the isolated rotation component is purely biomechanical or also influenced by movement familiarity cannot be answered in the present context.

3. EXPERIMENT B

3.1. Methods

3.1.1. Participants

A sample of 24 male participants with a mean age of 23.4 years (*SD* = 3.3 years) was assessed using the automated apparatus. All 24 participants had either recently received or were currently pursuing a university degree. Handedness was assessed using the Edinburgh Handedness Inventory version by Salmaso and Longoni (1985). One participant was left-hand dominant; all other participants were right-hand dominant. Participants received either study-credits or 20 EUR for their participation. Participants were assigned to one of eight conditions, balancing the order of mixed and blocked sessions, task-cue color assignment (kept constant across sessions for each participant), and the order of blocks in the blocked condition (rule first or plan first). The assignment was matched for age. Instructions were given in German. The experimenter confirmed language fluency.

3.1.2. Materials and Procedure

The same equipment and general experimental procedure as in Experiment A was used. The experiments differ in two points. First, the real object version of the RPMC experiment was used in *both* sessions. Second, rather than manipulating action-mode per session (real vs. pantomime) Experiment B sessions varied task switching conditions by presenting either a mixed or a blocked versions of the experiment per session (within-subjects design).

In the blocked version of the experiment, participants received instructions and training trials only for the block that would immediately follow (rule block or plan block) and received the other half of instructions and training trials in the second half of the experiment. In Experiment B half of the participants received the blocked version of the RPMC paradigm in the first session, while the other half received the mixed version first.

3.1.3. Data Analysis

The same analyses as in Experiment A were conducted on Experiment B data with the condition factor (mixed/blocked) replacing the action-mode factor (real/pantomime). Thus, the ANOVAs for each of the dependent variables RT, MT, and rotation time, contained the main effects of task (rule/plan), grip (pronated/supinated), hand (non-dominant/dominant), and condition (blocked/mixed) as well as the task*condition interaction.

3.2. Results Experiment B

3.2.1. Reaction Time

The ANOVA of RTs showed a significant main effect of task, with participants showing slower mean RTs in the plan task than in the rule task. The planned task comparisons in each condition revealed significant task differences in both the blocked condition, $t_{(23)} = 2.48$, $p = 0.021$, and the mixed condition, $t_{(23)} = 4.18$, $p < 0.000$. There was also a main effect of condition, with slower mean RTs in the mixed version of the experiment than in the blocked version. The significant main effect of grip showed slower RTs for underhand grips than for overhand grips. See **Figure 4** for plots of main effects. There was no significant effect of hand on RTs. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Full factorial data are given in Tables S2, S4.

3.2.1.1. Diffusion parameters

Condition had a significant effect on drift rate *v*, with a higher mean rate of information accumulation in the blocked condition than in the mixed condition. The significant effect of task on drift rate, showed higher drift rates in the rule task, than in the plan task. The effect of task on non-decision time with longer

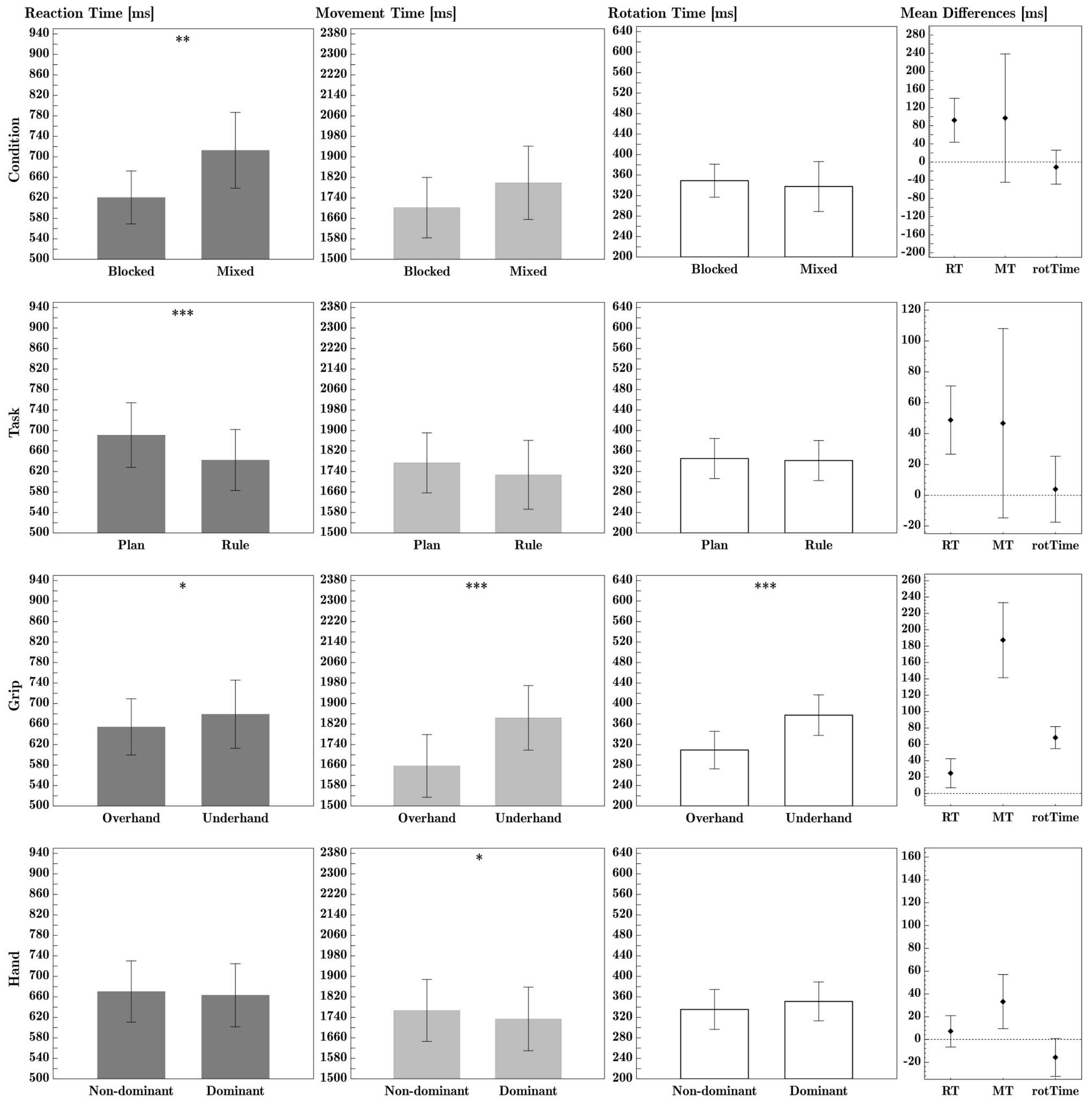

FIGURE 4 | Experiment B ANOVA main effects, for (from left to right column) reaction time, movement time and rotation time. Within-factor differences are shown in the far right column. All times are given in milliseconds. Error bars represent 95% confidence intervals. *, **, and *** denote significant differences with Holm-Bonferroni adjusted *p*-values $p_{adj} < 0.05$, < 0.01, and < 0.001, respectively. Calculation of mean difference times: Condition difference = (Mixed − Blocked); Task difference = (Plan − Rule); Grip difference = Underhand − Overhand); Hand difference = Non-dominant − Dominant. See **Table 3** for effect sizes and *p*-values.

t_0 in the mixed condition than in the blocked condition, was not significant after family-wise error correction. Condition*task interactions of diffusion model parameters are shown in **Figure 6**. See **Table 5** for drift diffusion ANOVA results and **Table 4** for drift diffusion parameter means and standard deviations.

3.2.2. Movement Time

The ANOVA revealed a significant main effect of grip (see **Figure 3**), with faster MTs in overhand grip trials than in underhand grip trials. Dominant hand MTs were significantly faster than non-dominant hand MTs. See **Figure 4** for plots of main effects. The interaction effect between condition and task (see **Figure 5**), was significant. *Post-hoc* testing indicates that in the blocked condition, there was no significant difference between mean MTs as a function of task, $p = 1$. In the mixed condition however, MTs in the rule task were significantly faster than MTs in the plan task, $p = 0.005$. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Full factorial data are given in Tables S2, S4.

3.2.3. Rotation Time

For technical reasons, rotation time data for one session of one participant were not recorded in the data file. That participant was excluded from rotation time analysis. The ANOVA of rotation times showed a significant main effect of grip, with faster mean handle rotation times in overhand trials than in underhand trials. This effect is shown in **Figure 3**. See **Tables 1**, **2** for main effect and interaction means, respectively. See **Table 3** for comprehensive ANOVA results. Full factorial data are given in Tables S2, S4.

3.2.4. Grip Errors

Pair-wise Wilcoxon comparisons showed that the number of grip errors significantly differed only in the plan, 98 total grip errors; $M = 4.08$, $SD = 3.99$, vs. rule, 38 total grip errors; $M = 1.58$, $SD = 1.79$, task comparison , $W(22) = 22.5$, $Z = 3.38$, $p < 0.001$.

3.3. Discussion Experiment B

In Experiment B we investigated whether task switching affects rule- vs. plan-based efficiency effects in the RPMC paradigm.

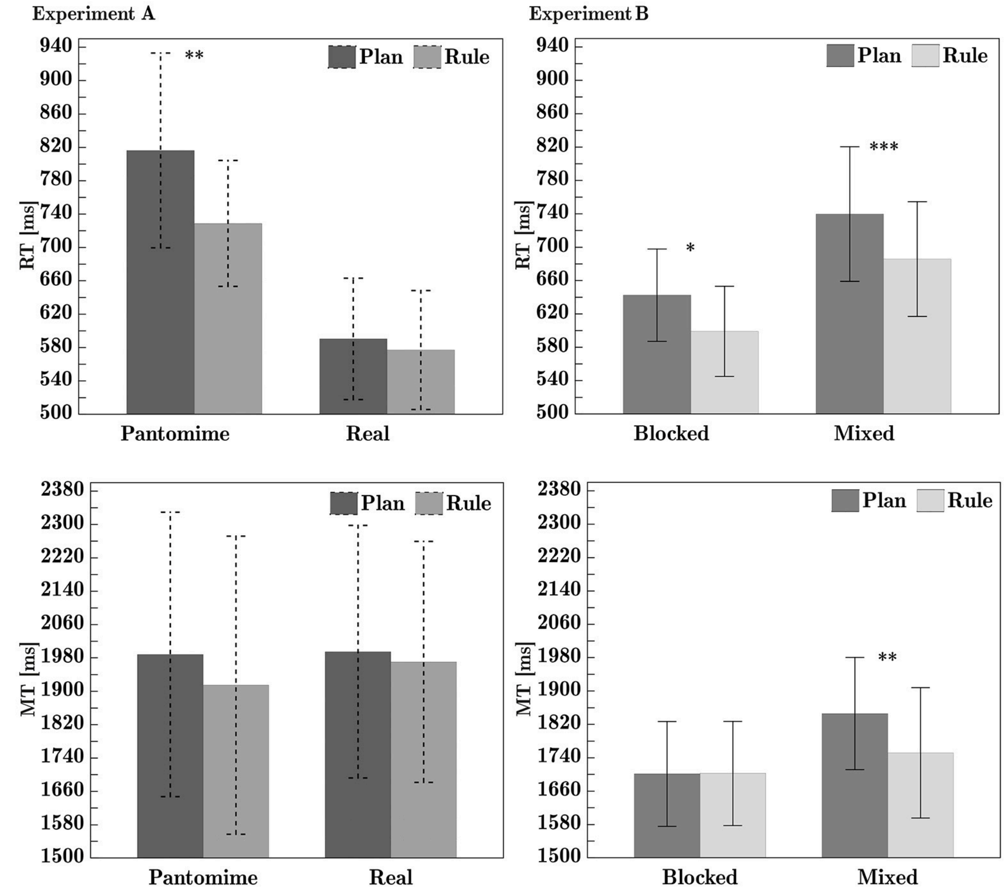

FIGURE 5 | Top row, left panel: Experiment A Mode*Task interaction for reaction time. Top row, right panel: Experiment B Condition*Task interaction for reaction time. Bottom row, left panel: Experiment A Mode*Task interaction for movement time. Bottom row, right panel: Experiment B Condition*Task interaction for movement time. All values are given in milliseconds. Error bars represent 95% confidence intervals. Only significant task differences within action-mode and condition are shown. RT differences were tested with t-contrasts. MT differences were tested with Bonferroni *post-hoc* tests. *, **, and *** denote significant differences with $p < 0.05$, < 0.01, and < 0.001, respectively. See **Table 3** for interaction effect sizes and p-values.

The η_p^2 effect sizes suggest that efficiency effects are dependent on the manipulated aspect that may affect different parts of the movement: movement initiation (RT) seems to be predominantly influenced by task and condition, movement (MT) by condition as well as grip type and hand, and the rotation-movement (rotTime) appears to be predominantly influenced by grip type.

3.3.1. Task and Task Switching Effects

As hypothesized, RTs in the rule task were significantly slower than RTs in the plan task, in line with the results of Randerath et al. (2013, 2015, 2017). Compared to flexible stimulus-response mappings in the plan task, the fixed if-then rules appear to predominantly facilitate the initiation phase of action.

Considering that participants made more errors in the plan task than during the rule task, while simultaneously showing slower reaction times in the plan task than in the rule task, this is strong evidence that the plan task is cognitively more demanding than the rule task. This is further supported by the significantly higher rate of information uptake in the rule task compared to the plan task as quantified by the diffusion parameter v.

Effects of task in the later stages of movement (MT) appeared to be modulated by the task switching condition. The significant interaction effect of condition and task on MTs indicates that during high cognitive load (i.e., during the mixed condition), if-then rules appear to reduce MT in comparison to plan-based action-selection. Interestingly, this advantage does not extend to the low cognitive background load condition (i.e., the blocked condition). Haji et al. (2015) used a surgical knot tying task in a study with medical students and measured movement efficiency under different cognitive loads. Students had to solve the task without visual feedback and in a constrained space. Using motion tracking, the researchers found knot tying performance, as measured by the mean number of movements per knot (lower is better) and time per knot (lower is better), to be better in the low cognitive load condition than in the high cognitive load condition. The cognitive load manipulation altered physical parameters of movement. The present experiment extends the evidence for effects of cognitive load on movement parameters by demonstrating the possibility of efficiency effects for relatively simple grasping tasks, i.e., even without the presence of additional constraints or reduced visual feedback.

The hypothesis of faster RTs in the blocked version of the experiment compared to the mixed version of the experiment was corroborated and is best interpreted in the context of task switching. Frequent shifts between cognitive tasks have previously been shown to lead to an increase in RTs and/or error rate (Rogers and Monsell, 1995; Monsell, 2003). The difference between the number of grip errors made in the mixed compared to the blocked version of the experiment was not significant. This could be attributed to the task instructions which placed an increased emphasis on accuracy. As RTs in the mixed condition were longer than in the blocked condition it appears that the speed-accuracy trade-off (e.g., Fitts, 1966; Ollman, 1966; Pachella and Pew, 1968) was skewed toward accuracy. Contrary to expectations our diffusion model data failed to significantly account for task switching costs in the t_0 parameter after family-wise error correction. However, we did find the predicted higher drift rate in the blocked condition compared to the mixed condition. The effect of task switching on drift rate has previously been discussed by Schmitz and Voss (2012, 2014).

3.3.2. Effects of Hand and Grip Type

As in Experiment A, there were main effects of hand and grip on MTs with faster dominant than non-dominant hand MTs and slower underhand than overhand MTs. Also as in Experiment A, rotation times of underhand grips were significantly slower compared to overhand grips. However, counter to Experiment A and in line with Randerath et al. (2013), we found the predicted RT difference between overhand and underhand grips.

3.3.3. Experiment B Conclusion

Compared to Experiment A, in Experiment B the evidence for task based efficiency effects when interacting with real objects appeared stronger. While drift rates showed a similar pattern in both experiments, we found significant efficiency effects of rule-based action planning captured by reaction times in real object interactions, in Experiment B but not A. One key difference that could explain the larger task difference in RTs in Experiment B, compared to the Experiment A real condition, may lie in the way participants accomplished the tasks. In the following we provide a potential explanation. Firstly, the findings indicate that a portion of the grip selection process in the Experiment A real action-mode may have carried over into the movement phase, and thus reduced the effect of task in real action-mode RTs. An argument for less discrete grip selection during action initiation in Experiment A, is supported by the missing RT difference between overhand and underhand grips in Experiment A that subsequently appears to be present in the MT parameter. In line with this, **Figure 5** displays shortened RTs and prolonged MTs in the Experiment A real action-mode compared to the Experiment B mixed condition. Secondly, response caution (a parameter) in the Experiment A real action-mode compared to the Experiment B mixed condition appears to be lower (see **Figure 6**). This may indicate that participants in Experiment B responded more cautiously, going along with a larger potential for efficiency effects to show. This suggests that Experiment A participants, on average, placed more emphasis on the speed aspect of the task instructions than Experiment B participants. In line with this argument, it has been shown that the reduction in boundary separation is sensitive to the emphasis on speed (e.g., Zhang and Rowe, 2014). Future research might make use of response caution manipulations to determine the bounds of rule-based efficiency effects as they relate to individual response criteria.

4. GENERAL DISCUSSION

The RPMC paradigm demonstrates that for visually indistinguishable grasp-to-rotate actions, implementation intention based rules can induce quicker processing compared to the instruction to achieve a comfortable end position. However, although, measures of efficiency appear to produce a consistent pattern of results (i.e., shorter rule than plan RTs, higher rule than plan drift rates) the magnitude of this efficiency effect

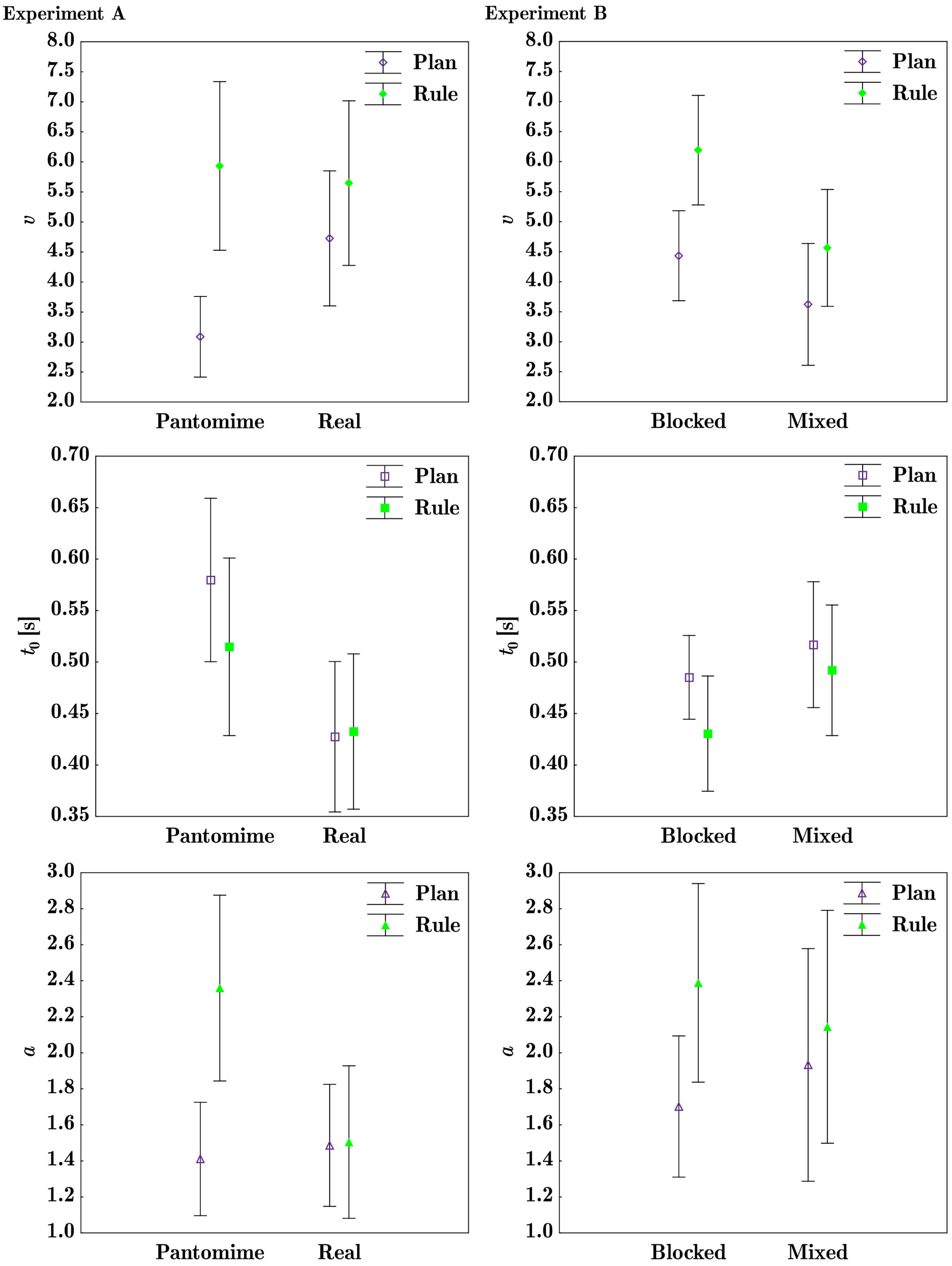

FIGURE 6 | The left column shows Experiment A action-mode*task interactions; the right column shows Experiment B condition*task interactions for drift rate *v* (first row), non-decision time t_0 (in seconds, second row), and decision boundary separation *a* (bottom row). See **Table 5** for effect sizes and *p*-values.

does not appear to be entirely robust across action-modes, task-switching conditions or measured parameters. Instead, the magnitude of the facilitating effect seems to be highly dependent on the present cognitive load.

Decomposition of RTs using diffusion modeling showed that the added imagery component in the pantomime task is well captured in the relative increase of the non-decision time parameter while accounting for changes in both rates of information accumulation and response criteria. Furthermore, diffusion modeling allowed us to describe how efficiency of the grip selection process is affected by the task manipulation, while controlling for other processes contained in reaction times, as well as individual response criteria.

As expected, we observed advantages of rule-based over plan-based responses in both the pantomime and real object condition (Experiment A) as well as within a real object mode for both a blocked and a task switching condition (Experiment B). However, this effect appeared stronger under conditions for which enhanced difficulty is suggested: the pantomime action-mode and the task-switching mode, respectively. Further, in Experiment A, higher efficiency of rule-based action was only found for RTs in the pantomime action-mode, but not in the real object action-mode. However, drift rates appeared to be more sensitive in detecting differences between tasks across action-modes. As expected, participants showed significantly higher drift rates v in the rule task than in the plan task, supporting the notion of facilitated processing in the fixed response mapping condition irrespective of action-mode and task-switching condition.

Given the described variability of efficiency effects modulated by cognitive load, the question arises what this means with respect to the idea of a meaningful application of implementation intention based rules to facilitate motor cognitive tasks in the rehabilitative context of stroke patients. Determining components that can be manipulated in stroke patients to facilitate active behavior is critical to neurorehabilitation and may foster use-dependent plasticity (Kimberley et al., 2008). Stroke can go along with impaired cognitive functions and marked slowness of information processing (Hochstenbach et al., 1998; De Luca et al., 2017). It can compromise motor cognitive tasks affecting activities of daily living (Goldenberg, 2013; Buchmann and Randerath, 2017). We argue that implementation intention based rules may be particularly effective in improving the successful selection of actions in patients with difficulties therein. Thus, even though in healthy young adults efficiency effects of implementation intention based rules in the RPMC paradigm are reduced in actions involving real objects, patients with difficulties in action planning may still profit significantly. We propose that by implementing such rules the load on the already limited cognitive resources may be reduced in patients with stroke. Spared cognitive resources may thereby be used to support active behavior. Whether these efficiency effects simply reflect a reduction of load on the same processes or whether both approaches to action target different mechanisms needs further clarification. In any case, both mechanisms could be helpful. Future studies including clinical populations will have to investigate this point.

The utility of rule-based approaches seems likely, for example, for limb apraxia patients with parietal lobe lesions and associated deficiencies in planning based movements. The idea is underpinned by a recent functional imaging study that demonstrated that rule-based actions put less strain on neural networks of action- selection particularly in parietal regions (Randerath et al., 2017).

Intriguingly, studies which have combined imaging methods with diffusion modeling have found evidence accumulation correlates in parietal regions (e.g., van Vugt et al., 2012), and frontoparietal networks (for a review see Mulder et al., 2014). Future imaging studies using the RPMC paradigm could use diffusion model-based decomposition of task performance to localize process specific neural substrates, as has been done in other high-level cognitive neuroscientific subfields (for an overview see Forstmann et al., 2016). Doing so may aid in the identification of patient populations that could benefit from rule-based action planning.

Lastly, the present research contributes to the literature on implementation intentions by investigating motor planning in a controlled laboratory setting, and thereby fills a crucial gap in the literature. On the one hand, past laboratory research on implementation intentions has largely relied on intellectual or cognitive tasks such as reacting to stimuli with button presses or evaluating pictures and recent studies using physical tasks (Bieleke and Wolff, 2017; Thürmer et al., 2017) focused on endurance performance only. On the other hand, applied implementation intention research has largely investigated complex behaviors, such as eating more healthily (Adriaanse et al., 2011; Vilà et al., 2017). The present research investigates basic motor planning in the laboratory with a task that closely resembles a real challenge for neuro-rehabilitation patients: Grasping and interacting with an object. Thereby, this research combines high external validity with high experimental control. Moreover, the present research contributes to the recent efforts of modeling how exactly implementation intentions achieve performance improvements (Stewart and Payne, 2008; Janczyk et al., 2015).

AUTHOR CONTRIBUTIONS

JS: Analysis, interpretation, study design, apparatus development, data acquisition, and writing. SS: Data acquisition, study design, analysis, writing. JT and JR: Study design, interpretation, writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2018.00309/full#supplementary-material

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