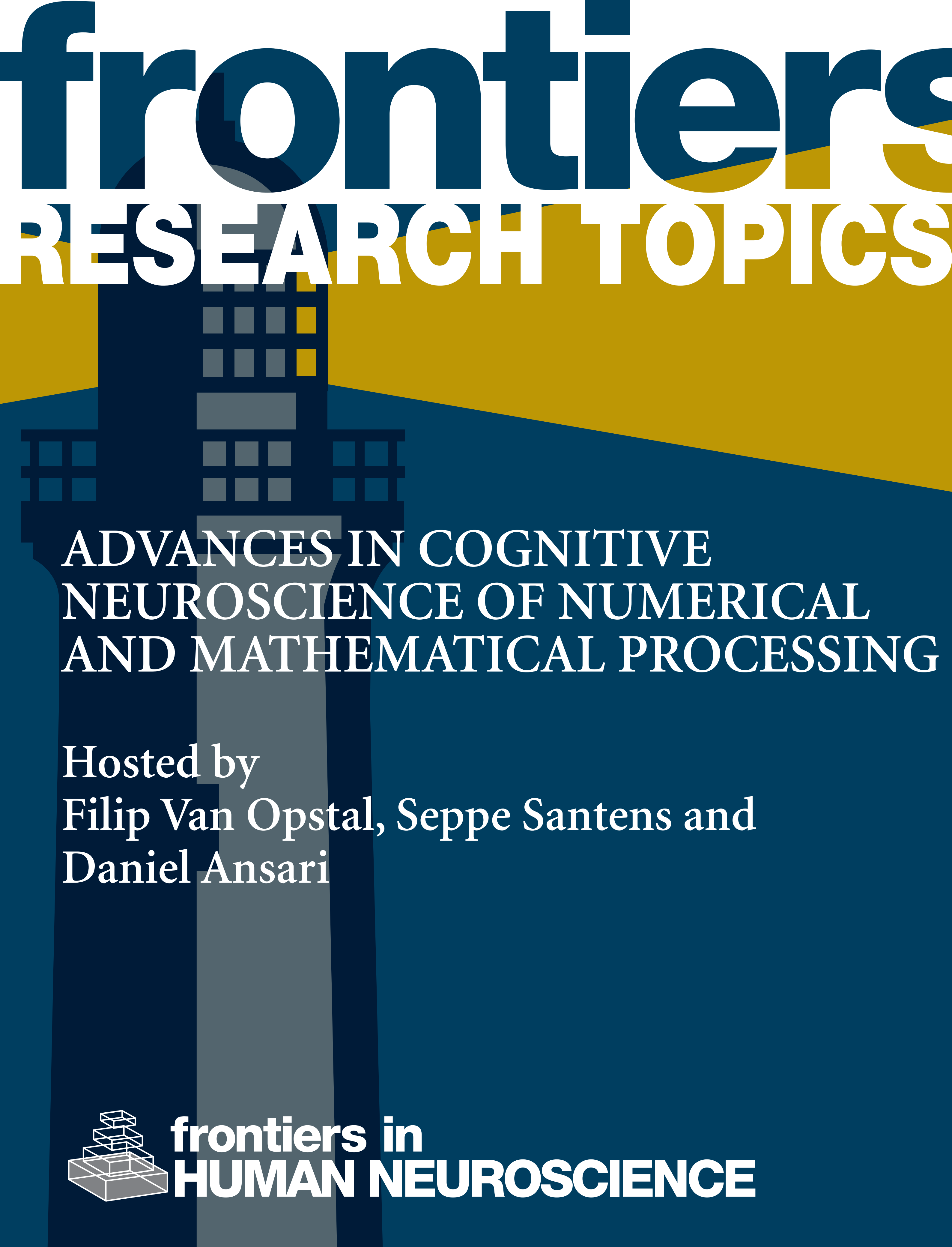

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ADVANCES IN COGNITIVE NEUROSCIENCE OF NUMERICAL AND MATHEMATICAL PROCESSING

Hosted by
Filip Van Opstal, Seppe Santens and Daniel Ansari

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HUMAN NEUROSCIENCE

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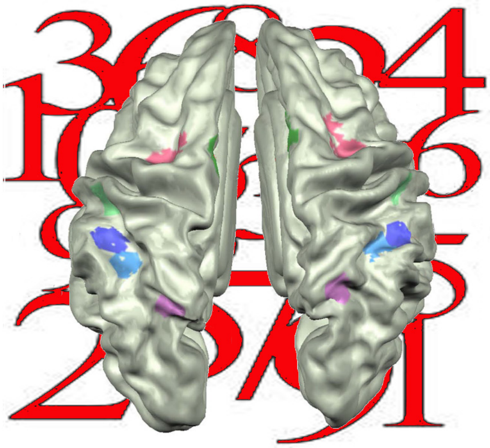

In this special issue, the most recent advances in the domain of numerical cognition will be presented. During the last decades, our understanding of how numbers are processed increased dramatically with the arrival of different imaging techniques and neurophysiological experiments in humans and monkeys. We are now starting to build up a clearer picture of how numbers are represented in the brain, how this representation develops in the course of a lifetime, how numbers are embedded in other cognitive features like attention, spatial memory, etc., and how this eventually leads to our capability to perform complex mathematics. Ultimately, this accumulation of knowledge might provide us with an understanding of why numbers are problematic for some people. This special issue deals with all aspects of numerical cognition: findings on the basic neural responses to magnitudes, the link between numbers, space, time, attention, action, etc., mathematical processing, numerical development, in healthy and clinical populations. This special issue solicits contributions from the field of neurobiology, neuropsychology, and behavioral and computational neuroscience that will increase our understanding of the neural mechanisms underlying numerical cognition.

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EDITORIAL
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The numerate brain: recent findings and theoretical reviews on the neurocognitive foundations of number processing

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Numbers are omnipresent in our daily life. They are used to denote the date or time, the value of products, or to indicate the speed at which you drive your car. Indeed, numbers are part of our everyday life and as adults we use and manipulate them seemingly without any effort. But how do we do this? How is the meaning of numbers acquired and represented? And what brain mechanisms subserve the representation of number and mental operations involving numbers that guide our actions?

The burgeoning field of "Numerical Cognition" seeks to provide answers to these kinds of questions. Researchers in this field seek to understand the representation and the neural correlates of basic numerical processes and how these basic processes relate to higher-level mental operations of these foundational representations, such as mental arithmetic. It should be clear that the relation between the most elementary numerical skill, such as the extraction of the numerosity of a set of elements, and solving mathematical equations is quite complex and rather difficult to investigate. In fact, the many faces of numbers further complicate the matter. A number is a highly abstract symbol that can represent different things. It can symbolize a magnitude (cardinality; "4" could indicate the number of children you have) or the rank (ordinality; "4" could also refer to your youngest child when placed in chronological order). The same number can also be written in many forms: 4 is equal to IV, to "Four," and to ••••. Furthermore, in mathematics, numbers can also be positive or negative, small or large, natural, or decimal numbers. Numerical cognition research aims at understanding how these different conceptions of numbers relate to each other and how we develop an understanding their meaning.

Over the last few decades these issues have been addressed by studying numerical skills in different animal species, human infants, and adults. However, the result of these years of focused research has not provided us with definite answers. Although some models of numerical cognition have dominated the research for many years, the basic representation of numbers remains debated until today. Even the mechanisms behind the most basic numerical skills, such as the comparison of two numbers, lack agreement in the research community. Indeed, the true nature of most of the commonly observed effects in simple numerical tasks, e.g., subitizing, the distance effect, the size congruity effect, or the SNARC-effect, remains obscure. On the other hand, the repeated observation of these effects in numerous studies indicates that they are genuine and that they could hold the key toward a proper understanding of number processing.

It appears that more agreement is reached on the brain areas related to basic number processing. Many brain imaging experiments in humans and monkeys, and studies on patients with brain lesions have shown a strong involvement of the horizontal segment of the intraparietal sulcus (hIPS) in number processing. However, despite the apparent agreement of a central role of the hIPS in number processing, the specificity of this area for numbers and the exact role of the hIPS in a more elaborate number processing brain network is still under investigation.

This Research Topic for *Frontiers in Human Neuroscience* covers a wide range of the remaining issues in numerical cognition. It discusses how numerical quantity is extracted from small sets of stimuli (Hyde, 2011), how the extraction of numerosity can be related to a system that extracts information from continuous dimensions (Henik et al., 2012) or to sensory-motor experiences (Ranzini et al., 2011). Furthermore, the causes of developmental dyscalculia are evaluated and the role played by symbolic (i.e., Arabic numerals) and non-symbolic (i.e., arrays of dots) in understanding this specific difficulty in mathematical processing is discussed (Noel and Rousselle, 2011). Research in the field of numerical cognition has grappled for to understand exactly how numerical and spatial processing are related. A number of contributions in this research topic shed further light on the association between number and space (Koten et al., 2011; Priftis et al., 2012; Van Dijck et al., 2012; Zorzi et al., 2012). Another question concerns the differences between automatic and intentional processing of number and the brain processes that mediate these different levels of number processing (Cohen Kadosh et al., 2012). Indeed, rather than confining number processing to a single area of the brain, a more elaborate network might be involved when a more elaborate number processing is needed, as in the processing of negative numbers (Blair et al., 2012), or doing mathematics (Grabner et al., 2011).

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Two systems of non-symbolic numerical cognition

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Studies of human adults, infants, and non-human animals demonstrate that non-symbolic numerical cognition is supported by at least two distinct cognitive systems: a "parallel individuation system" that encodes the numerical identity of individual items and an "approximate number system" that encodes the approximate numerical magnitude, or numerosity, of a set. The exact nature and role of these systems, however, have been debated for over a 100-years. Some argue that the non-symbolic representation of small numbers (<4) is carried out solely by the parallel individuation system and the non-symbolic representation of large numbers (>4) is carried out solely by the approximate number system. Others argue that all numbers are represented by the approximate number system. This debate has been fueled largely by some studies showing dissociations between small and large number processing and other studies showing similar processing of small and large numbers. Recent work has addressed this debate by showing that the two systems are present and distinct from early infancy, persist despite the acquisition of a symbolic number system, activate distinct cortical networks, and engage differentially based attentional constraints. Based on the recent discoveries, I provide a hypothesis that may explain the puzzling findings and makes testable predictions as to when each system will be engaged. In particular, when items are presented under conditions that allow selection of individuals, they will be represented as distinct mental items through parallel individuation and not as a numerical magnitude. In contrast, when items are presented outside attentional limits (e.g., too many, too close together, under high attentional load), they will be represented as a single mental numerical magnitude and not as distinct mental items. These predictions provide a basis on which researchers can further investigate the role of each system in the development of uniquely human numerical thought.

Keywords: number, cognition, representation, ERP, fMRI, attention, memory

INTRODUCTION

The brain has at least two systems for representing number non-symbolically; however, these systems represent number in qualitatively different ways (see Feigenson et al., 2004 or Piazza, 2010 for reviews). The approximate number system encodes an imprecise estimate of the numerical magnitude, or numerosity[1], of a set of objects (see Gallistel, 1990; Butterworth, 1999; Nieder and Dehaene, 2009; Dehaene, 2011 for reviews). The mental representations formed by this system can be used to compare and combine numerical magnitudes. Importantly, this system uses one mental symbol to summarize the set. In contrast, the parallel individuation system forms a distinct mental symbol for each item (see Carey, 2009 or Scholl, 2002 for reviews). This system privileges spatiotemporal information to initiate a mental index, or object file, for each item. Although inherently non-numerical in nature, these representations afford numerical content by retaining information about numerical identity – mentally stored items can be compared on a one-to-one basis with visible objects in the scene to detect numerical matches or mismatches.

These systems are further characterized by their contrasting limits (see Feigenson et al., 2004 for a review). The imprecision of the approximate number system systematically increases as numerosity increases. As a result, the ability to estimate numerosity has no particular upper bound, but discrimination of any two numerical quantities follows Weber's Law, as it is a function of the ratio between the two quantities to be compared. In contrast, the ability to simultaneously represent and track objects through parallel individuation is limited to only a few items (usually about 3–4)[2]. Representations through parallel individuation afford more fine-grained numerical discriminations than those of the approximate number system if numbers are within the range of this system, but comparisons fail when the limits of this system are surpassed. The signature limits of ratio and capacity have allowed researchers to find evidence of the two numerical systems across

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[1] As a reviewer aptly pointed out, a distinction should be made between "number" as a mathematical entity and "numerosity" as a cardinal value of a set of items. When referring to primitive numerical representations, specifically those of the approximate number system, I am referencing the notion of a cardinal value of a set of items, or numerosity, rather than "number" as a mathematical entity. In the paper I also use the term "non-symbolic number representation" to refer to "numerosity."

[2] It should be noted that the current proposal could be applied to a fixed slot/item-limited model (e.g., Luck and Vogel, 1997; Cowan, 2001; Zhang and Luck, 2008) or resource/information-limited model of working memory (e.g., Alvarez and Cavanagh, 2004; Wilken and Ma, 2004). This debate is intentionally avoided here because it seems to be unresolved in the literature more generally.

age-groups and species, suggesting these systems are innate, arise very early in human infancy, and are shared with a wide variety of non-human animals.

One difficulty in understanding the nature and function of these systems has been in specifying the conditions under which each system is engaged. This difficulty has been historically compounded in experiments that contrast the processing of small (<~4) and large numbers (>4; e.g., Jevons, 1871; Kaufman et al., 1949; Trick and Pylyshyn, 1994). Jevons (1871) was the first to demonstrate empirically a dissociation between small and large number processing by asking subjects to count the number of beans tossed into a shallow pan. He showed that enumeration of 1–4 items was perfectly accurate, while errors increased as the number of items to be enumerated increased beyond 4. The phenomenon of precise, accurate, and seemingly instantaneous enumeration of a small number of items, in contrast to the slower, more inaccurate process for larger number of items, was later termed "subitizing" to distinguish it from counting (Kaufman et al., 1949).

The most striking dissociations seen between small and large numbers, however, come from human infants without symbolic counting abilities (e.g., Xu, 2003; Lipton and Spelke, 2004; Feigenson and Carey, 2005; Wood and Spelke, 2005). For example, after watching an experimenter sequentially place 1 food item in one bucket and 2 food items in a different bucket, human infants reliably search in the bucket with 2 food items (e.g., Feigenson et al., 2002; Feigenson and Carey, 2003, 2005). In similar comparisons of 1 vs. 3 and 2 vs. 3, they search in the bucket with numerically and physically more food items. However, in cases where more than 3 items are placed in any given bucket (e.g., 2 vs. 4; 1 vs. 4), infants are not able to reliably choose the bucket with more food items. These highly replicable failures, seen in a variety of paradigms with infants (e.g., Feigenson and Carey, 2003, 2005; Xu, 2003; Lipton and Spelke, 2004), combined with the processing dissociations in human adults (e.g., Jevons, 1871; Kaufman et al., 1949; Trick and Pylyshyn, 1994), have led some to propose that parallel individuation is engaged exclusively when processing sets with a small number of objects (1–3 or 4) and the approximate number system is engaged exclusively when processing sets with larger numbers of objects (>4; see Simon et al., 1995; Uller et al., 1999; Feigenson et al., 2002, 2004; Xu, 2003; Lipton and Spelke, 2004; Ansari et al., 2007; Van Herwegen et al., 2008). Under this view, what will be called here the "two systems view," the parallel individuation system is specialized to represent small numbers and the approximate number system is specialized to represent large numbers; numerical range determines when each system will be engaged.

Other evidence, however, suggests that the approximate number system operates over both large and small numbers (e.g., Moyer and Landauer, 1967, 1973; Meck and Church, 1983; Brannon and Terrace, 1998; Cordes et al., 2001; Cantlon and Brannon, 2006). For example, Cordes et al. (2001) showed that when adult subjects were asked to tap a table a given number of times while under articulatory suppression, their tapping of both small and large numerosities showed the systematic variability characteristic of the approximate number system. Similarly, Brannon and colleagues have shown that the ability to order small and large numerosities is a function of the ratio between the numbers to be ordered in non-human primates and adults under articulatory suppression, suggesting the approximate number system is operating over the entire range of numbers used (e.g., Brannon and Terrace, 1998; Cantlon and Brannon, 2006). In addition, most formal mathematical models of non-symbolic number representation in the brain assume all numbers are represented by the approximate number system (e.g., Meck and Church, 1983; Church and Broadbent, 1990; Dehaene and Changeux, 1993; Zorzi and Butterworth, 1999; Verguts and Fias, 2004; Nieder and Merten, 2007). This type of evidence has led some to adopt, what will be called here the "one system view" of numerical cognition. Importantly, proponents of the "one system view" do not deny the existence of the parallel individuation system, but contest that the approximate number system operates over the entire range of numbers, large and small. From this view, it is unclear exactly what conditions elicit differential representations from parallel individuation and approximate number. One proposal is that both types of representations are formed over sets simultaneously and under some conditions representations of parallel individuation override those of approximate numerosity when acting on the world (e.g., Cordes and Brannon, 2009; Burr et al., 2010, 2011). Another proposal is that object file representations are formed over small numbers initially and then these representations are converted to approximate numerosity representations (e.g., Cordes and Brannon, 2009).

In sum, most researchers agree that humans and many non-human animals possess both the ability to represent a set as an approximate numerical value or as distinct object files. Furthermore, there is accord that the ability to represent individual items in parallel is limited to only several items at a given moment. Until recently, however, the field has disagreed as to the conditions that activate each system and, in particular, whether these systems are specialized for small and large numbers. Recent work in psychophysics and, in particular, cognitive neuroscience, with non-human animals, human infants, and human adults has provided empirical evidence for the distinctness of these systems in the brain and a better understanding of the experimental conditions that elicit representations from each system[3]. Furthermore, this recent work suggests a hybrid view of the "two systems" and "one system" views by delineating the conditions under which each system is engaged and the cognitive constraints that underlie this delineation.

RECENT INSIGHTS

DISTINCT REPRESENTATIONS

Recent work has directly contrasted small and large number processing using common measures and methods. This work has shown that under many conditions small numbers are represented differently than large numbers. For example, a recent event-related potential (ERP) study showed that human adults spontaneously encode number while passively viewing dot arrays; however, small and large numbers are encoded differently (Hyde and Spelke, 2009). Small numbers (1–3 items) evoke an early posterior parietal response (N1) that scales with the number of individuals in the set irrespective of the number in the array that preceded it.

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[3] The current literature review focuses on work conducted within the last 5 years.

In contrast, large numbers evoke a later, mid-latency component over posterior parietal scalp (P2p) that scales with the ratio of numerical change between successive sets (Hyde and Spelke, 2009). These signatures mirror the behavioral signature limits of the two systems (Feigenson et al., 2004) to suggest that the approximate number system and the parallel individuation system are being differentially engaged over large and small numbers under these conditions. Similarly, in an ERP number comparison task, Libertus et al. (2007) also observed distinct early signatures for small numbers (Libertus et al., 2007).

Psychophysics has further confirmed the qualitative distinction between small and large number processing (Revkin et al., 2008; Piazza et al., 2011). For example, Revkin et al. (2008) showed that estimates of large and small numbers differ in reaction time, accuracy, and the distribution of the answers. Furthermore, individual variability in the small number range does not correlate with individual variability in the large number range and individual differences in subitizing capacity do not correlate with individual differences in large non-symbolic number comparison precision (Revkin et al., 2008; Piazza et al., 2011). Together these results suggest small number subitizing relies on a distinct cognitive mechanism from estimation of larger numbers and that, under these conditions, small numbers are not being represented as approximate numerical magnitudes.

It is reasonable to posit that the distinct signatures for small compared to large numbers arise from the extensive practice human adults have at enumerating, visualizing, and remembering small numbers of items, 1–3, compared to larger numbers of items like 8 or 32. As mentioned above, previous work showing differences in small and large number processing in non-human animals and pre-verbal human infants suggests that this may not be the case. Recent work has strengthened the case for an innate difference between small and large number processing, as opposed to an experiential difference. For example, Cordes and Brannon (2009) used a habituation method to show that young infants fail to dishabituate to changes in number that cross the small/large number divide and it is only when the ratio is increased to a 1:4 ratio (e.g., 2 vs. 8) that infants succeed at discriminating a large and a small number. Furthermore, Hyde and Spelke (2011a), using the same ERP measure and similar passive viewing methods as in adults, showed distinct brain signatures for small and large numbers in human infants that parallel those observed in adults (Hyde and Spelke, 2009, 2011a; but see Izard et al., 2008). These results in infants without any numerical education, symbolic number practice, and/or spoken language present a strong case for innate differences between small and large number processing that are not dependent on formal numerical experience or language.

Directly comparing small and large numbers has also resulted in qualitative and quantitative dissociations in animals evolutionarily far removed from humans (Agrillo et al., 2007; Rugani et al., 2008, 2010; Piffer et al., 2011). For example, Agrillo et al. (2007) showed that fish are able to discriminate between two social groups of peers at a closer ratio (e.g., 2 vs. 3 or 3 vs. 4) when groups are made up of smaller numbers of fish, compared to the ratio at which they can discriminate between two social groups that contain larger numbers of fish (Agrillo et al., 2007). Furthermore, like human infants, fish fail to discriminate between numbers that cross the small/large divide (3 vs. 5) until the ratio difference is increased (Piffer et al., 2011). Similarly, young chickens have been shown to discriminate between two small numbers, but fail to discriminate between a large and a small number, or two large numbers unless the ratio between them is increased substantially (Rugani et al., 2008, 2010). These results, in species far removed from humans, further support the idea of innate representational differences between small and large number processing.

Together this evidence suggests that the "one system view" does not always hold. That is, approximate number representations are not always formed over sets of small numbers of objects under experimental conditions where they are clearly formed over large numbers.

DISTINCT NEURAL MECHANISMS

Recent neurophysiological and neuroimaging work also suggests that the distinct neural and behavioral signatures of the two systems arise from anatomically distinct brain regions. For example, Hyde and Spelke (2011b) used the low resolution electromagnetic tomography (LORETA) source localization algorithm to estimate the neural origin of ERP signatures of small and large number processing. Early, distinctly small number ERPs signatures (modulation by cardinal value) appeared to arise from extrastriate visual regions including superior and lateral portions of visual cortex and later small number processing appeared to arise from right temporal–parietal junction (RTPJ) and left parietal regions, whereas distinctly large number processing (modulation by numerical ratio of change between successive images) appeared to arise primarily from right intraparietal regions.

In a similar vein, Ansari and colleagues used functional magnetic resonance imaging (fMRI) to measure the brain response as subjects performed a number comparison task. They found that small number comparisons elicited an increase activity in the RTPJ, whereas large number comparisons elicited a decrease in activity in the RTPJ and an increase in activity in the parietal occipital sulcus (Ansari et al., 2007). Similar RTPJ activity has independently been observed in anther study contrasting enumeration of small and large numbers (Vetter et al., 2011). Both groups attribute the small number RTPJ activity to stimulus driven attention, that is not present or not present to the same extent in large number processing.

Finally, a complementary line of functional neuroimaging work suggests encoding of individual objects may occur within the IPS as well (Culham et al., 1998, 2001; Xu and Chun, 2006; Xu, 2009). More specifically, recent work suggests that inferior IPS activity scales with the number of objects in scene up to about three to four and then plateaus while the superior IPS responds to differences in object identity, but not number. These results suggest that portions of the inferior IPS support the initial selection and individuation of a limited number of objects from a scene (up to about four), in contrast to the lateral occipital complex and the superior IPS, which seem to support object identification (Xu and Chun, 2006; Xu, 2009).

In sum, recent neuroimaging results further contest the "one system view" that approximate number representations are formed over small numbers, as small number processing under many conditions elicits qualitatively distinct patterns of brain activity in anatomically distinct regions compared to activity elicited for large numerosities.

DIFFERENTIAL ENGAGEMENT OF ATTENTION

The functional neuroimaging and electrophysiological evidence provided above points to the possibility that small and large numbers differentially recruit attention. Specifically, ERP markers of attentional processing (e.g., N1 component) are modulated in qualitatively different ways for small and large numbers; early ERPs increase as number increases for small but not large numbers (e.g., Hyde and Spelke, 2009, 2011a,b). Furthermore, small and large number processing recruit at least some distinct brain regions (Ansari et al., 2007; Vetter et al., 2011; Hyde and Spelke, 2011b). The particular brain regions recruited distinctly for small numbers (or modulated by small, but not large numbers), such as a portion of the inferior IPS and RTPJ (see Corbetta and Shulman, 2002 for a review), have been linked to attentional effects whereas the regions uniquely identified for large numbers (or that respond more to large than small numbers) and some of the regions that respond to both large and small numbers have not necessarily been linked to attentional effects. The most recent and exciting work contrasting small and large numbers has experimentally tested what the above reported results imply, attention and/or working memory operate differentially over small and large numbers.

One line of this work looks at the role of attention and working memory in enumeration of small and large numbers (subitizing small numbers vs. counting or estimation of larger numbers). For example, one recent study showed that subitizing (rapid, quick, and near perfect enumeration of small numbers) is inhibited during a dual task with high attentional load but estimation is not (Burr et al., 2010; but see Vetter et al., 2008 for contradictory results). Another study showed that individual differences in subitizing correlated with individual differences in working memory, but not individual differences in estimation abilities (Piazza et al., 2011). Furthermore, holding several items in working memory while jointly attempting to subitize reduced the capacity limit of the subitizing range. Importantly, the same working memory dual task does not impair estimation abilities (Piazza et al., 2011). Impairments to subitizing are also observed using an attentional blink paradigm (Egeth et al., 2008; Olivers and Watson, 2008; Xu and Liu, 2008). Interestingly, increasing viewing eccentricity also decreases enumeration accuracy for small numbers but not large numbers (Palomares et al., 2011).

Another exciting line of work investigating the role of attention in numerical processing has looked at neural adaptation to number. This research has typically shown that the brain adapts to the numerosity of large but not small numbers (Burr and Ross, 2008). One recent study, however, looked at the ability of the brain to adapt to numerosity under attentional load. Adaptation to numerosity was observed for small and large numbers when subjects were under high attentional load but was only seen for large numerosities when subjects are not under an attentional load (Burr et al., 2011). Another recent study measured the electrophysiological brain response to passive viewing of small and large numbers under conditions within and beyond the limits of attention (Hyde and Wood, 2011). When subjects viewed small numbers presented beyond the resolution limits (smaller individual items, crowded, and in the periphery) or under high attentional load (performing an attention demanding rapid serial visual presentation task) the brain signatures of the approximate number system and not parallel individuation were observed for small numbers. In contrast, when items were viewed within the resolution of attention (larger, further spaced items) or under no additional attentional load (same visual stimuli with no dual task), the brain signatures of parallel individuation, but not the approximate number system, were observed for small numbers.

These results, like those presented above, contest the "one system view" by showing that when stimuli are presented within the limits of attention, approximate number representations are not formed over small numbers. However, these results also contest the "two systems view" to suggest that the two systems are not specialized for small or large numbers *per se*, but rather are engaged differentially depending on the nature of the visual stimuli presented and the attentional or working memory constraints in place (Burr et al., 2010, 2011; Hyde and Wood, 2011; Piazza et al., 2011).

A UNIFYING THEORY OF THE TWO NUMERICAL SYSTEMS

Recent studies bring together findings of both similarities and differences between small and large number processing to suggest: (1) The two systems are qualitatively and anatomically distinct. (2) The two systems are not specialized for small and large numbers. (3) The two systems are crucially affected by limits to early visual, attentional, and working memory. These novel results unify the "one system view" and the "two systems view" to provide an account of the conditions under which each system is engaged over a set of items.

General constraints on visual processing, attention, and working memory determine if a given set of items is represented as individual object files or as an approximate numerical magnitude (Burr et al., 2010, 2011; Hyde and Wood, 2011; Piazza et al., 2011). Small numbers are often represented distinctly from large numbers because they fall within the limits of the brain to individuate and track simultaneously (see Feigenson et al., 2004). In fact, when items are presented within the limits of the brain to form object files, parallel individuation may be the default. Importantly, under these conditions, small numbers do not appear to be represented as approximate numerical magnitudes. That is, none of the evidence accrued to this point suggests that small numbers are spontaneously represented both through the parallel individuation system and through the approximate number system. Dichotomous and qualitatively different representations explain striking developmental failures in infants and some non-human animals to distinguish numbers that cross the small/large divide, as well as the differential behavioral and brain signatures of small and large number processing observed in infants and adults (Feigenson and Carey, 2003, 2005; Xu, 2003; Cordes and Brannon, 2009; Hyde and Spelke, 2009, 2011a,b).

Large numerosities, in contrast, always fall beyond the limits of the brain to encode, remember, and simultaneously track distinct individual items. Therefore, the default, at least for simultaneously presented large quantities, appears to be representation as a numerical magnitude. Furthermore, if small number sets are presented beyond the limits of the brain to encode as individual object files (e.g., too close together) or if sufficient attentional/working memory resources are not available (e.g., because resources are tied up in another task), it appears that small numbers are also represented as approximate numerical magnitudes like large numbers. This can explain the cases where processing of small quantities shows the signatures of approximate number representation (Cordes et al., 2001; Burr et al., 2011; Hyde and Wood, 2011). For example, articulatory suppression, attentional blink, or dual task paradigms, which demand substantial attentional resources, often lead small number processing to show variability consistent with the approximate number representation (e.g., Cordes et al., 2001).

This proposal can also potentially explain studies showing infant success at discriminating numbers across the small/large boundary (evidence for common representation of small and large numbers; e.g., Cordes and Brannon, 2009). The experimental manipulation through which successful discrimination across the small/large boundary is achieved (increasing the ratio between the small and large number from 2 vs. 4 to 2 vs. 8) also correlates with a substantial decrease in the spacing of individual objects (as a by-product of the non-numerical controls employed). It is plausible, given the evidence provided above, that the decrease in spacing of objects in the 2 vs. 8 condition, not the increase in ratio in and of itself, exceeded the limits of the infant visual attention system to encode the items as object files, resulting in representation of the set as an approximate numerical magnitude. If this were correct, decreasing the spacing of objects in the 2 vs. 4 condition beyond the attentional limits to form object files, would also produce success (without increasing the ratio).

Figure 1 presents a graphical representation of how the current proposal might work. When presented with a set of items, numerical representation through parallel individuation occurs if attention selects individual items and subsequently forms a mental symbol, or object file, for each individual item in the set. Each object file is then stored in working memory and the specific properties of each item can then be bound to the mental representation of each specific individual (e.g., size, color, type, category, meaning, etc.). If attention is not able to select individuals because the limits are surpassed (e.g., too many, they are too close together, engaged in another attention demanding task, etc.), the set is summarized by a single mental symbol and properties of the set, or ensemble statistics, will be calculated, approximate numerosity being one property of the set.

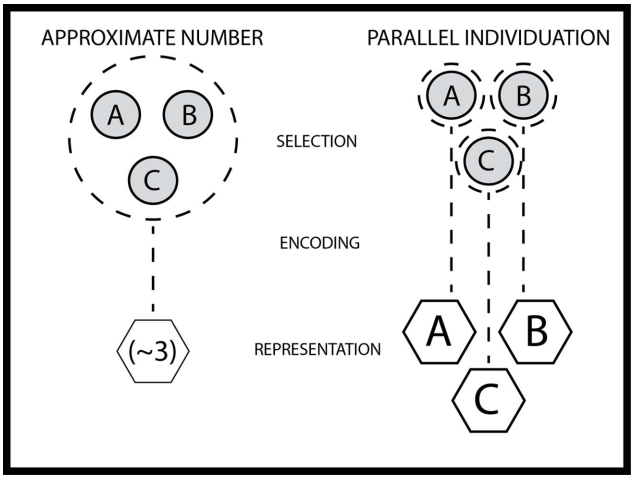

FIGURE 1 | Schematic depiction of number representation through the approximate number system and the parallel individuation system.

LIMITATIONS AND FUTURE DIRECTIONS

One open question is if number can be simultaneously represented through parallel individuation and the approximate number system over a single set or subset of objects[4]. None of the evidence accrued to this point suggests that the same items are being simultaneously represented as individual object files and as an approximate numerical magnitudes. On the contrary, the evidence to date suggests that early attentional selection and subsequent cognitive encoding determine whether a given set of objects will be spontaneously represented as set of individual object files or as a set with an approximate numerical magnitude (e.g., Burr et al., 2011; Hyde and Wood, 2011). However, such a dichotomous process, if it exists, is certainly only a bias of spontaneous mental representation of number. It is certainly the case that a set of objects can be reanalyzed and encoded differently. This undoubtedly occurs in real world situations where our initial analysis of the visual scene has to be quickly revised or refocused for our current action.

Most of the work cited presents items simultaneously and often quickly. Less explored is the representation of number during sequential processing. Although sequential presentation has been used developmentally (e.g., Feigenson and Carey, 2003, 2005) and has produced some interesting similarities and differences to simultaneous processing, it has not been adequately explored and directly contrasted with simultaneous presentation to study numerical cognition. Sequential presentation is important for future work to determine if the same numerical signatures of the two systems hold and if attentional and working memory constraints similarly operate.

It is also unclear if the current proposal generalizes to other sensory domains such as audition and somatosensation. Systematic studies comparing numerical cognition across sensory modalities would be helpful in elucidating potential sensory-specific contributions to the mental representation of numerosity. A promising recent line of work appears to show that limits on parallel individuation/object file representation are not restricted to perceptual processes, as they extend to the planning of actions as well (Gallivan et al., 2011). However, at this point, it is still unclear if the general principles established for visual numerical representation apply equally or differentially to other sensory modalities. For example, Wood and Spelke (2005) showed similar development from 6 to 9 months in precision of representing number of actions (number of times a puppet jumped) as have been shown with visual stimuli (e.g., Xu, 2003). More specifically, 6-month-old infants can tell the difference between 4 and 8 jumps, but not between 4 vs. 6 or 2 vs. 4 jumps. On the other hand, vanMarle and Wynn (2009) found that infants could discriminate 2 from 4 tones,

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[4] This question is different from the question of whether number can be estimated for multiple sets in parallel, which evidence suggests is the case (Halberda et al., 2006).

but not 2 from 3 tones. They interpreted this behavioral pattern to suggest infants were using the approximate number system in the auditory domain and that the limits of this system are similar in the auditory and visual domains (because infants of this age fail at 2 vs. 3 ratios but not at 1:2 ratios with large numbers in the visual domain). While it is certainly the case that infants could have been engaging the approximate number system here and this is consistent with the proposal above, it is unclear why they succeed at 2 vs. 4 in the auditory domain, but fail in the visual domain (e.g., Xu, 2003; Cordes and Brannon, 2009). A better understanding of the attentional limits in simultaneously representing individuals in other sensory domains may provide some insight into this puzzle.

Here we display work showing a variety of constraints on attentional resources change the way the brain represents objects numerically. Beyond the scope of this paper, however, there is a vast literature showing that attention can be divided into different sub-types, namely bottom-up and top-down attention, and different types of attention are constrained by different factors (see Corbetta and Shulman, 2002 for a review). For example, top-down attentional processing is constrained by increasing perceptual or working memory load, while bottom-up attentional processing is constrained by stimulus degradation (e.g., Lavie and de Fockert, 2003; Lavie, 2005; Awh et al., 2006). It may also be the case that perceptual or cognitive factors that facilitate grouping items vs. treating them individuals interact with attention to bias the way in which numerosity is represented. For example, Gestalt principles such as proximity, similarity, or closure (for a review see Todorovic, 2007) or cognitive factors such as whether items are seen as an "object" (e.g., Egly et al., 1994) may differentially bias how attention is allocated, thereby influencing whether items will be represented as a group with an approximate numerical magnitude instead of individual items. Future work on numerical cognition should carefully consider the role and/or interaction of top-down and bottom-up attentional processing, as well as the particular environmental constraints present, in the representation of numerosity through the two systems.

Future work should also investigate potential distinctions and interactions between attention and working memory in non-symbolic number representation. Early ERP signatures suggest attention is distributed differentially when a set of items is encoded as individual object files compared to when it is encoded as an approximate numerical magnitude (Hyde and Spelke, 2009, 2011a,b; Hyde and Wood, 2011). Other work on remembering and tracking objects shows sensitivity in later processing to remembering and tracking objects (e.g., Luck and Vogel, 1997; Drew and Vogel, 2008). One question for future work would be how these early attentional effects interface with working memory representations of non-symbolic number downstream. More generally, numerical cognition may provide an avenue to further investigate attention and working memory, their respective limits, and the interplay.

Finally, certain insights gained from this proposal, namely early attentional constraints determine the nature of number representation, must be considered when investigating the role of each system in the development of uniquely human numerical and mathematical abilities. The field has shown a surge of excitement from recent work linking the precision of approximate number representations with numerical and mathematical achievement in school (Halberda et al., 2008; Gilmore et al., 2010; Piazza et al., 2010; Bugden and Ansari, 2011); Furthermore, at least one leading proposal as to how children acquire natural number concepts implicates parallel individuation as a crutch in this process (Le Corre and Carey, 2007; Carey, 2009). Future work should carefully examine individual differences in parallel individuation, approximate number representation, as well as the influence of individual differences in attention and working memory, to form a better understanding of the role each of these cognitive abilities plays in forming uniquely human numerical and mathematical concepts.

CONCLUSION

The emerging picture from recent work is that the two established systems of non-symbolic number representation do not operate in isolation from other cognitive and perceptual limits, nor do they appear to operate in parallel of each other. Rather, numerical information is encoded differentially from a set of objects based on what is presented and what else the brain is doing.

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Quantities, amounts, and the numerical core system

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Numerical cognition is essential to many aspects of life and arithmetic abilities predict academic achievements better than reading (Estrada et al., 2004). Accordingly, it is important to understand the building blocks of numerical cognition, the neural tissue involved, and the developmental trajectories. In the last two decades research has made impressive strides forward in studying numerical cognition and brain mechanisms involved in arithmetic. This advance was marked by suggestions of a numerical core system that can be characterized as a set of intuitions for quantities innately available to humans (Brannon et al., 2006) and animals (Cantlon and Brannon, 2007). We suggest that another system, evolved to perceive and evaluate non-countable dimensions like size or amount of substance may be important for the evolution of the numerical system and numerical abilities. The current opinion article examines this idea and the possible interplay between, on the one hand perception and evaluation of continuous dimensions and, on the other, the numerical system.

NEUROCOGNITIVE BASIS FOR QUANTIFICATION

Several behavioral effects have been well documented in the field of numerical cognition. Amongst them are: subitizing, counting, and the distance effect. The first and second refer to the processes involved when participants are asked to enumerate – report the number of items in an array. Here, performance is best described as a biphasic graph: their reaction time (RT) rises slowly, between 40 and 100 ms per item, up to four items, and then rises steeply at a rate of 250–350 ms per item (Jevons, 1871; Trick and Pylyshyn, 1994). It seems that four items (or less) can be grasped almost simultaneously with no effort; this is termed subitizing (Kaufman et al., 1949). In contrast, for five to nine items, participants are engaged in an effortful counting process. The third behavioral effect, the distance effect, arises when participants are asked to compare two arrays of dots, or two numerals. RT decreases with increase in the distance between the to-be-compared stimuli. This numerical distance effect was first reported by Moyer and Landauer (1967) who suggested that people convert written or auditory numbers into analog magnitudes. The effect has been reported by many other researchers under various conditions (Banks et al., 1982; Dehaene, 1989; Link, 1990; Tzelgov et al., 1992; Schwarz and Heinze, 1998). Further research showed these effects (e.g., subitizing, counting, and distance) can be found in infants and animals. For example, the numerical distance effect has been found in children (Sekuler and Mierkiewicz, 1977; Mussolin and Noël, 2007; Holloway and Ansari, 2008; Landerl and Kölle, 2009), and in primates (Brannon, 2003; Cantlon and Brannon, 2006). In addition, the various effects are compromised in developmental dyscalculia (DD) or mathematical learning disability (MLD) (for subitizing and counting: Koontz and Berch, 1996; Geary et al., 1999; Landerl et al., 2004; Moeller et al., 2009, for the distance effect: Price et al., 2007; Rousselle and Noël, 2007; Mussolin et al., 2010). Finally, many reports have suggested involvement of the parietal lobes and in particular the intraparietal sulcus (IPS) in numerical cognition (Dehaene et al., 2003; Fias et al., 2003; Ansari et al., 2006; Cohen Kadosh et al., 2007a).

This accumulated body of results led to a widely accepted view of an innate domain-specific foundation for arithmetic. In particular, it has been claimed that there is a core numerical system, the basis of which is the ability to perceive and manipulate discrete quantities (e.g., enumeration of dots) (Ansari, 2008; Dehaene, 2009; Butterworth, 2010; Piazza, 2010). In addition, it has been conjectured that arithmetic disability involves a domain-specific deficit in the capacity to enumerate (Butterworth, 2010; Piazza, 2010). However, careful scrutiny of the literature suggests that to achieve a comprehensive picture of numerical cognition other factors need to be examined.

CAREFUL EXAMINATION OF CORE QUANTIFICATION

A survey of the literature raises several interesting observations; (1) similar to their sensitivity to discrete quantities (e.g., enumeration of dots), infants show sensitivity to non-countable continuous dimensions like area (Brannon et al., 2006), line length (de Hevia and Spelke, 2010), and size (Lourenco and Longo, 2010). Mix et al. (2002) surveyed the literature on quantification in infancy and early childhood and suggested that the literature provides no clear-cut evidence that infants use numbers to perform quantitative tasks. Moreover, they summarized that there is evidence that infants respond to amount of substance, rather than discrete numbers, in what had seemed to be numerical tasks. (2) Developmental trajectories similar to those with numbers (i.e., the size of the distance effect has been found to decrease over developmental time Sekuler and Mierkiewicz, 1977) have been shown in other areas (see example for the Stroop effect reported by Schiller, 1966) and seem to rely on domain-general rather than domain-specific abilities (Holloway and Ansari, 2008). During development, language may provide a medium that bridges between core domain-specific systems (Munkholm, 2001; Spelke, 2003; Platt and Spelke, 2009). Last but not least, (3) numbers are intimately associated with non-countable dimensions (e.g., size, brightness). Numerical values and physical sizes interfere with one another – the size congruity effect (Henik and Tzelgov, 1982; Tzelgov et al., 1992; Cohen Kadosh et al., 2008c) and the same apply to the relationship between numbers and brightness (Cohen Kadosh and Henik, 2006). Importantly, Lourenco and Longo (2010) reported a size congruity effect in infants that were 9 months old. They presented convincing evidence for an intimate relationship between numerosity and size; infants who learned to expect an association between color and size of objects also expected to see a similar association between color and numerosity. Moreover, the size congruity effect is compromised in DD (Rubinsten and Henik, 2005, 2006).

This short review of the literature suggests that other factors might contribute to the development of the number sense. In particular, it is possible that the need and ability to evaluate non-countable dimensions (e.g., sizes or amounts) helped to develop or to improve the domain-specific "core knowledge" of arithmetic, which extracts numerosity of sets (Dehaene, 2009).

SIZES, AMOUNTS, AND THE NUMERICAL SYSTEM

The size congruity effect is dependent on numerical proficiency. Irrelevant numerical values will not affect relevant physical-size judgments unless the participant is proficient with the numerical system. Consequently, it was found that the size congruity effect develops with age (Rubinsten et al., 2002). In recent years this effect was employed to study proficiency with the number system and automaticity (i.e., processing even when not part of a task requirement) in numerical processing (Rubinsten et al., 2002; Cohen Kadosh et al., 2007a; Szucs and Soltesz, 2007). Recent research indicates that it involves the IPS: It was found to be deficient in a patient who suffered from a brain injury in the IPS (Ashkenazi et al., 2008) and imaging studies (fMRI) have shown that it is correlated with IPS activation (Cohen Kadosh et al., 2007a, 2008b; Szucs and Soltesz, 2007). Interestingly, other aspects of objects like brightness (Cohen Kadosh et al., 2008a), ordinal position, and time also involved the IPS (Simon et al., 2002; Walsh, 2003; Cantlon et al., 2009).

Those with DD show deficient processing in size congruity (Rubinsten and Henik, 2005, 2006) and temporary lesioning of the IPS by transcranial magnetic stimulation (TMS) produce a DD-like pattern of the size congruity effect (Cohen Kadosh et al., 2007b). Importantly, DD subjects show deficiency not only in size congruity but also in other dimensions that interact with numbers like brightness and height (Rubinsten and Henik, 2005). Hence, it is conceivable that the basis of DD or MLD or its precursor lies with a difficulty in processing and evaluation of sizes or amounts. In a recent article, Bugden and Ansari (2011) examined the relationship between the size congruity effect and math performance in first and second grade children. They reported that size congruity did not predict math performance. This is not in line with our expectations. However, this might be due to the restriction of the range of the predictor (i.e., size congruity) or math performance or both. Alternatively, it is possible that size congruity might predict performance in older children because of its dependence on math proficiency.

Imaging data as well as behavioral results led to suggestions that "…countable and uncountable quantity…should be represented with the same kind of symbols (mental magnitudes)…to determine behaviorally important decisions" (Gelman and Gallistel, 2000), and that important computational demands of an action system (reaching, grasping) are the basis for the involvement of the parietal lobes in comparative judgment tasks (Walsh, 2003). Namely, it has been suggested that the parietal lobes reflect computational demands of the brain dorsal system involved in perception for action (Goodale et al., 1991; Goodale, 2000). However, Cantlon et al. (2009) have recently suggested that the ability to evaluate magnitudes (e.g., size) might underlie the development of the numerical system. This is in line with the general view suggested in the current proposal. Namely, the evolution of the dorsal brain system might have been dependent on the ability to compute size and size differences. A neurocognitive system that handles this aspect of cognition (evaluation of size or amount) might have been instrumental for the development of the occipito-parietal dorsal brain system (perception for action). This same system (evaluation of size or amount) helped develop or improve the numerical system.

Interestingly, recent works on perception of objects using various size and distance illusions suggested that perceived rather than retinal size modulates activation of early visual areas (i.e., v1; Murray et al., 2006; Sterzer and Rees, 2006; Fang et al., 2008). Moreover, according to Goldfarb and Tzelgov (2005), perceiving size, on the basis of monocular distance cues, is automatic and modulates numerical processing. It is possible that size is processed very early both in terms of visual feature extraction and in terms of timing in the visual stream. This information is fed forward to the parietal lobes (and other brain structures) to serve other systems and goals (e.g., the dorsal brain system).

In a recent article, Piazza (2010) reviewed two early pre-verbal systems: the approximate number system (ANS) and the object tracking system (OTS). She suggests that children are equipped with both systems before symbolic learning takes place, each system is based on dedicated neural circuits, and each undergoes a separate developmental trajectory. Piazza concludes that the ANS rather than the OTS is crucial for the development of numerical cognition. The ANS represents numbers in an approximate fashion. However, the ANS (and OTS) involves enumeration of discrete quantities and obeys Weber's law. The current proposal focuses on the ability to evaluate and perceive continuous and non-countable properties. Needless to say, evaluation of continuous variables is approximate by definition. Similarly, Gebuis and Gevers (2011) recently suggested that continuous visual properties, like area subtended by dot arrays, modulate performance that was earlier suggested to rely on numerosity.

A PRECURSOR OF THE NUMERICAL SYSTEM?

We suggest that routines and neural structures built for size judgments were made available to other systems (e.g., language), through evolution, due to the need to develop an exact numerical system. We have focused on the existence of non-countable representations and the ability to perceive and evaluate sizes or amounts. We suggest that the ability to perceive and evaluate sizes might be a more primitive system that was exploited, throughout the years, as the basis for the development of the number sense and numerical abilities. Whether this system was "…hi-jacked to perform judgments along a new dimension (e.g., number)" (Cantlon et al., 2009), was shaped by cultural needs (Dehaene, 2005; Dehaene and Cohen, 2007), or became accessible to the numerical system through evolution (Rozin, 1976) is not clear. But this system might be the antecedent of the numerical system. Note that this fits in with the idea put forward by Piaget that continuous spatial extent serves as the antecedent to a child's concept of discrete numbers (Feigenson, 2007). Going back to the discussion of the OTS (Piazza, 2010), it seems that object individuation is a necessary process on the way to a discrete numerical system. Within the framework of the current proposal, it is important to find out how organisms moved from evaluation and perception of continuous non-countable properties to perception and enumeration of individual objects, or more generally, how these two abilities affected one another.

Interestingly, the visual system is characterized by a similar arrangement. Humans have two co-existing visual pathways. In addition to the primary, evolutionarily younger, geniculo-striate system there exists an evolutionarily older system – the retino-tectal pathway. These two systems have somewhat different roles but are connected and have mutual effects (Henik et al., 1994). The evolutionarily older system deals mainly with spatial aspects of vision and connects to the parietal lobes. Interestingly, the evolutionarily older system is critical in blind-sight when the primary visual system is damaged (Rafal et al., 1990). As alluded to earlier, it is quite possible that the number and the size/amount systems evolved to coexist, similar to these two visual systems.

Alternatively, it is possible that evaluation of size/amount is not based on a separate system but rather only one system exists. This could be a system that processes both numerosity and sizes or amounts. Both aspects of this system evolved together due to changing natural requirements. Namely, moving between the requirement to develop an enumeration ability under certain circumstances and the requirement to evaluate sizes (note Helmholtz's unconscious inference, which explains size constancy) under other conditions. A situation like this would create a modular system whose modules are used interchangeably (Kashtan and Alon, 2005).

In order to gain a comprehensive picture of numerical cognition, there is a need to study the ability to perceive and evaluate sizes and amounts and their relationship to the development of the numerical system.

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Graspable objects shape number processing

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The field of numerical cognition represents an interesting case for action-based theories of cognition, since number is a special kind of abstract concept. Several studies have shown that within the parietal lobes adjacent neural regions code numerical magnitude and grasping-related information. This anatomical proximity between brain areas involved in number and sensorimotor processes may account for interactions between numerical magnitude and action. In particular, recent studies have demonstrated a causal role of action perception on numerical magnitude processing. If objects are represented in terms of actions (affordances), the causal role of action on number processing should extend to the case of objects affordances. This study investigates the relationship between numbers and objects affordances in two experiments, without (Experiment 1) or with (Experiment 2) the requirement of an action (i.e., participants were asked to hold an object in their hands during the task). The task consisted in repeating aloud the odd or even digit within a pair depending on the type of the preceding or following object. Order of presentation (object–number vs. number–object), Object type (graspable vs. ungraspable), Object size (small vs. large), and Numerical magnitude (small vs. large) were manipulated for each experiment. Experiment 1 showed a facilitation – in terms of quicker responses – for graspable over ungraspable objects preceded by numbers, and an effect of numerical magnitude after the presentation of graspable objects. Experiment 2 demonstrated that the action execution enhanced overall the sensitivity to numerical magnitude, and that at the same time it interfered with the effects of objects affordances on number processing. Overall, these findings demonstrate that numbers and graspable objects are strongly interrelated, supporting the view that abstract concepts may be grounded in the motor experience.

Keywords: number, object, affordance, action

INTRODUCTION

According to embodied and grounded cognition theories, all human knowledge is grounded into perception–action systems, through which sensory–motor experiences build up concrete and abstract concepts during lifespan (Barsalou, 1999; Gallese and Lakoff, 2005; Pecher and Zwaan, 2005; Pulvermüller, 2005). Whereas consistent evidence of this has been provided for concrete (i.e., non-abstract) knowledge (Barsalou, 2008), only few studies have suggested the possibility of an action-based development of abstract concepts (Boroditsky and Ramscar, 2002; Glenberg et al., 2008; Borghi and Cimatti, 2009; Casasanto, 2009; Borghi and Pecher, 2011; Pecher and Boot, 2011; Pecher et al., 2011). A specific case for the latter domain is given by numerical cognition.

Indeed, the concept of natural number is an example of abstract concept which develops primary through the sensory–motor experience of finger counting (Andres et al., 2008a; Fischer and Brugger, 2011). Children learn the meaning of number as an abstract concept which can be applied to a variety of different entities through the experience of counting on their hands. Finger counting may be relevant to the development of mathematical abilities as indicated by developmental studies (Noël, 2005), and its influence on numerical cognition persists through adulthood (Di Luca et al., 2006; Di Luca and Pesenti, 2008). Classic evidence of the relevance of hand-related abilities on numerical cognition comes from neuropsychological studies. For instance, both numerical and finger gnosis impairments typically co-occur in the Gerstmann syndrome (Gerstmann, 1940). In addition, the developmental Gerstmann syndrome (Kinsbourne and Warrington, 1963) is characterized, among other symptoms, by dyscalculia and constructional dyspraxia (Rourke and Conway, 1997), which might suggest a role of hand motor planning mechanisms in the development of numerical abilities. This association between the hand and the processing of numbers extends to the fundamental activity that humans can perform with their hands, which consists in grasping and manipulating objects.

At the cortical level, the human neural circuitry devoted to grasping is close to that of number processing (Simon et al., 2002). Indeed, a number of neuroimaging studies have found that numbers are consistently represented in the parietal cortex (Dehaene et al., 2003). However, the parietal lobes are crucial for a plurality of tasks, including attention, spatial cognition, sensory–motor integration, action planning, and control (e.g., Milner and Goodale, 1995; Culham and Kanwisher, 2001; Frey et al., 2005; Culham and Valyear, 2006). Most of these functions are organized in an anterior to posterior manner along the intraparietal sulcus (IPS, Simon et al., 2002). Their anatomical organization suggests that the neural mechanisms underpinning the hand-number relationship might lie in the IPS.

Of relevance for grasping action is the human anterior portion of the IPS (aIPS; for a review, see Castiello, 2005). Several parts of the human parietal cortex have homologous areas in the monkey brain (e.g., Culham and Kanwisher, 2001; Hubbard et al., 2005). However, it has been suggested that a part of the human aIPS, evolutionarily new, is related to the planning of grasping and principally to tool manipulation (Orban et al., 2006). Importantly, the circuitry for grasping, including parietal and premotor areas (Castiello, 2005), is recruited both during action execution and action observation (Grafton, 2009), during object observation and grasping execution toward the same object (Grèzes et al., 2003), and during the observation of manipulable objects (Gerlach et al., 2002). Perceiving objects – either man-made (Chao and Martin, 2000), familiar (Grafton et al., 1997), or tools compared to graspable shapes (Creem-Regehr and Lee, 2005) – triggers the activation of both the dorsal stream, in particular in the IPS (Culham and Valyear, 2006), and the ventral one, more specifically in the ventral premotor cortex (PMv; for a review, see Johnson-Frey, 2004). Neuroimaging studies, thus, suggest that the properties of an object are coded by brain areas involved both in its observation and manipulation (for a review, see Martin, 2007). Concerning aIPS, a recent study by Cavina-Pratesi et al. (2010) has suggested that aIPS processes intrinsic (i.e., shape and size) rather than extrinsic (i.e., location) properties of the object (in accordance to Jeannerod, 1981).

With reference to numbers, many neuroimaging studies have suggested that the IPS – in particular, the horizontal segment of the IPS (hIPS) – is crucial for the semantic representation of numerical quantity (Dehaene et al., 2003; Piazza et al., 2004). For instance, its activation is specific for numbers compared to letters or colors (Eger et al., 2003), and it is modality independent (e.g., Piazza et al., 2007; for a different view, see: Cohen Kadosh and Walsh, 2009). Together with the representations of numbers, the representations of other physical dimensions, such as size, are associated to the IPS activation (Fias et al., 2003; Pinel et al., 2004; Cohen Kadosh et al., 2005), and interactions between the processing of different magnitudes have been shown, first of all, by behavioral studies (e.g., Henik and Tzelgov, 1982). These similarities have suggested that numerical and non-numerical magnitudes may be processed by a generalized magnitude system, which is domain-independent, and mediated by the parietal lobe (a theory of magnitude, ATOM: Walsh, 2003; Bueti and Walsh, 2009). Most importantly, the cognitive processes and the neural mechanisms underlying this system might subserve sensory–motor transformations for action (Walsh, 2003; Bueti and Walsh, 2009). In this sense, some aspects of the number processing might be embedded in the process of integration of the aspects of the environment that are relevant for action. As additional evidence of common circuits for number and action, some PET and fMRI data converged in indicating that, during numerical tasks, not only parietal but also precentral areas are activated, similarly to what commonly observed during hand-related activity (Pesenti et al., 2000; Zago et al., 2001).

The anatomical organization of the IPS might account for recent behavioral studies showing that numerical magnitude modulates hand movements, specifically hand grasping. This was shown by Andres et al. (2004) in a parity judgment task with grip closure/opening response modality: increasing or decreasing speed in initiating closure or opening grip movements respectively was a function of increasing digit magnitude. Similar results were observed when participants were required to respond to digit stimuli using a precision or a power grip (Lindemann et al., 2007; Moretto and Di Pellegrino, 2008): response with precision grip was faster for numerically small digits whereas response with power grip was faster for larger digits. In addition, Andres et al. (2008b) have observed that numerical magnitude modulates kinematic parameters of grasping. Specifically, they found that when participants were required to grasp an object and put it backward or forward in function of the parity of a digit presented on its surface, grip aperture during grasping was larger for numerically larger digits than for smaller ones.

Number influences on action were observed even in the absence of an explicit motor action, when action processes were mediated by objects perception (Badets et al., 2007; Chiou et al., 2009). The assumption that objects are represented in terms of actions, i.e., in terms of affordances (Gibson, 1979; Ellis and Tucker, 2000), is widely shared in the literature. Gibson (1979) defined affordances as properties in the environment that are relevant for an organism's goals: for example, a banana offers us the possibility to be grasped and eaten. According to Gibson, affordances are registered directly by our perceptual system. Recent views of affordances differ in part from Gibson's view, indicating affordances as brain representations of action possibilities, i.e., the result of previously stored perception–action experiences (Ellis and Tucker, 2000). Badets et al. (2007) firstly explored number effects on perceived affordances asking participants to evaluate whether they could grasp a visually presented object of variable size. Crucially, participants judgment was modulated by the magnitude of the digit they were required to name one second before. Interactions between numerical magnitude and action in absence of an explicit movement were also observed in a dual-task where a parity judgment and a consequent action judgment on an object were performed (Chiou et al., 2009). Response was faster for small digits associated to objects which could be grasped with a precision grip, and for large digits associated to objects which could be grasped with a power grip.

The studies described above mainly showed that numerical magnitude could modulate action processes, without however revealing whether action could likewise influence the processing of numbers. Importantly, recent studies have found that the interactions between numbers and action are bidirectional, describing effects of action observation on number processing (Badets and Pesenti, 2010). Badets and Pesenti (2010) asked participants to indicate the odd or the even digit in a pair depending on the opening or closing hand movement presented before or after the presentation of the digits pair. Beside an overall interaction between movements and digit magnitude, they observed a specific slowing of reaction times for large digits following closing movements performed by biological hands compared to fake hands. Authors proposed that the effect arose because a large number constitutes a non-expectable outcome for grasping, as only small numbers are associated to hand grasping (possibly as consequence of the human constraint on counting up to small quantities on the one hand). This study suggests that the way in which sensory–motor processing modulates number processing has a causal role and is not simply a cognitive epiphenomenon (see also Badets and Pesenti, 2011). It is worth noting that, in almost all these studies, the numerical tasks employed allowed only an implicit activation of the numerical magnitude (parity judgment task: Andres et al., 2004; Lindemann et al., 2007; Andres et al., 2008b; Chiou et al., 2009; Badets and Pesenti, 2010: Experiments 1 and 3; Moretto and Di Pellegrino, 2008: Experiment 1; digit color judgment task: Moretto and Di Pellegrino, 2008: Experiment 2; digit naming task: Badets et al., 2007), thus permitting to claim that number magnitude and action interactions should be considered, at least to some degree, automatic.

The present study aims at investigating the effects of action on number processing when action is mediated by objects. Badets and Pesenti (2010) have shown that observing grasping hand postures influences the processing of numbers. However, to our knowledge no previous study so far has demonstrated that observing manipulable objects, which suggest grasping actions, impacts on number processing. This is crucial also in light of the fact that different motor-related mechanisms might be implied while observing objects and while observing actions with objects. Recent behavioral evidence (Liuzza et al., 2011) obtained with a categorization task demonstrated the existence of different mechanisms underlying observation of grasping hand postures and observation of objects. Results showed that observing the image of a grasping hand priming an object activated motor information. However, this was not the case when the object alone was presented, without a prime evoking motor information. These results suggest the involvement of different motor-related underpinnings during action and during object observation. Indeed, previous studies on the monkey premotor cortex (Murata et al., 1997; Di Pellegrino et al., 1992) and further neurophysiological and brain imaging studies on humans (for a review see Rizzolatti and Craighero, 2004) have distinguished two different systems, the Mirror neuron system and the Canonical neuron ones. While mirror neurons fire both when a grasping action is perceived and performed, canonical neurons fire when a given action is performed and when the subject sees an object upon which to perform an action. In light of these results, we intend to verify whether not only observation of grasping hand postures, but also observation of objects elicits motor information interacting with number processing.

In order to explore this issue, we performed two experiments. In Experiment 1 we adopted the same paradigm of Badets and Pesenti (2010). Instead of finger movement mimicking an opening or closing movement, in our study the stimulus was an object, either graspable or ungraspable. We hypothesized that the presentation of graspable objects would modulate the number magnitude processing. Specifically, we expected that the motor information conveyed by graspable objects would prime small numbers or would interfere with large ones. In Experiment 2 we investigated how a task-irrelevant hand action modulates object–number interactions. The paradigm was the same of the previous experiment, except for the fact that participants were required to hold an object in their hands during the execution of the task. We hypothesized that this modulation would elicit an interference between the object–number interaction and the concurrent action of holding. This prediction is based on the fact that, being the grasping/motor system already engaged by the parallel task, there would be no room for the occurrence of an interaction between affordance and numerical magnitude. We mainly based our analysis on the numerical magnitude effect, consisting in quicker responses for smaller than larger numbers (Moyer and Landauer, 1967; see also Loetscher and Brugger, 2007). The numerical magnitude effect is an index of the number processing, as it is supposed to reflect the way in which numbers are encoded as magnitudes in a mental representation (metaphorically conceivable as a mental number line; Restle, 1970), and specifically it reflects the more accurate representation of small numbers compared to large ones. Observing modulations of the numerical magnitude effect induced by object affordances would confirm the hypothesis that affordances “shape” number processing.

EXPERIMENT 1

METHOD

Participants

Thirty-two undergraduate students from the University of Bologna (11 males and 21 females; mean age: 23.3 years; 6 left-handed) took part in the experiment for course credits. All participants had normal or corrected-to-normal vision, gave written informed consent and were naive to the purpose of the experiment.

Apparatus and stimuli

Participants sat in front of a 17″ monitor (the eye-to-screen distance was approximately 50 cm). E-Prime 1.1 software was used for presenting stimuli and collecting responses. The experimental stimuli consisted of digit pairs preceded or followed by an object. One pair of small (2 and 3) and one pair of large (8 and 9) Arabic numerals were used. The digit position within a pair (left or right) was counterbalanced. There were 32 objects either graspable or ungraspable (see **Table 1**), presented in small (mean pixel 82 × 138, mean cm 3 × 5) or large (mean pixel 382 × 494, mean cm 13 × 16) format. Even if the objects image size was not exactly comparable to the objects actual size, the distinction between small and large objects reflected real size disparities, as small images referred to objects that are in the reality smaller than the larger ones. Note that in the case of graspable objects, different sizes should induce different kinds of grip: power or precision grips for large or small objects, respectively. Thus, there were four categories (graspable-small objects, graspable-large objects, ungraspable-small objects, ungraspable-large objects), with eight objects for each category. Three ratings studies were preliminarily carried out to match target objects for familiarity and visual complexity, and to differentiate them for their graspability (i.e., participants evaluated an object based on whether it was possible or not to lift it with the hands and move it from one place to another). In each rating, 20 different and independent raters judged the degree of the characteristic under exam of the objects on a seven-point Likert scale (with 1 = minimum and 7 = maximum). Response means were entered into a 2 × 2 within-subject ANOVA with the factors

Table 1 | The 32 objects of Experiment 1.

Graspable objects		Ungraspable objects	
Small	**Large**	**Small**	**Large**
Almond	Ball	Atom	Bell
Chili	Cabbage	Bee	Bench
Clippers	Case	DNA	Bush
Drawing pin	Coconut	Exclamation mark	Cactus
Match	Courgette	Flame	Hedge
Nut	Dipper	Ink stain	Roadsign
Pastry	Eggplant	Question mark	Rock
Ticket	Vase	Snow flake	Traffic lights

Object type (graspable vs. ungraspable) and *Object size* (small vs. large). Results showed that graspable and ungraspable objects were matched for familiarity and visual complexity ($p = 0.44$ and $p = 0.30$, respectively), and that they significantly differed for manipulability, $F(1,28) = 257.43$, $\text{MSE} = 0.43$, $p < 0.001$ (mean graspable objects = 6.36 and mean ungraspable objects = 2.64).

Procedure

The participants were required to recall and repeat aloud the odd or the even digit within a pair, preceding or following the target object, depending on the type of object presented (i.e., graspable vs. ungraspable). For example, if the target object was graspable, half of participants were asked to recall and repeat the odd digit, whereas if the object was ungraspable, they had to recall and repeat aloud the even digit. The reverse was true for the other half of participants. At the beginning of the experiment, participants were provided with this specific definition of graspability: "the object is graspable when you can lift and move it from one place to another with the hands" (for a similar definition, see: Borghi et al., 2007a, Experiment 2). The four-factors-of-interest were: *Order* (object–number vs. number–object), *Object type* (graspable vs. ungraspable), *Object size* (small vs. large), and *Numerical magnitude* of the digits pair (small vs. large number). The numerical magnitude and the object type were randomly presented, whereas the order of presentation, the object size, and the response mapping (graspable object – odd digit or graspable object – even digit) where counterbalanced across eight different blocks. Small and large objects were presented in different blocks to minimize the perceptual effects of size. Each session consisted of one practice block of 16 trials and one experimental block of 32 trials. Each trial began with a fixation point (+) displayed for 500 ms in the center of the screen. Then, in the object–number trials, a target object was shown for 1500 ms and followed by a pair of small or large Arabic digits, one odd and one even, which remained on the screen until a vocal response was recorded or 3000 ms had elapsed. In the number–object trials, a pair of small or large Arabic digits, one odd and one even, was shown for 1500 ms and followed by a target object which remained on the screen until a vocal response was recorded or 3000 ms had elapsed. The next trial began after an interval of 2000 ms (**Figure 1**). The order of blocks was counterbalanced between participants. After each block, participants could take a brief break. Overall the experiment consisted of 256 experimental trials and lasted about 60 min.

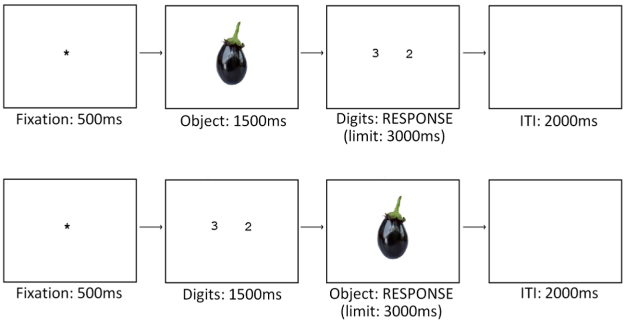

FIGURE 1 | Sequence of events in trials of object–number (on the top) and number–object (on the bottom) conditions. At the beginning of each trial, a fixation cross appeared on the center of the screen. The fixation cross was replaced by the first target (for example, an object in the object–number condition) and then by the second target (for example, a pair of digits in the object–number condition) until the vocal response execution or until 3000 ms had elapsed. After a delay of 2000 ms, the next trial began. Note that stimuli are not drawn to scale.

RESULTS

As instructions required participants to keep their hands on the table in a relaxed position, the data from two participants who did not follow the instructions were excluded from analyses. The resulting group consisted of 30 subjects. The incorrect responses were removed from the analysis (4.2%, range 0–10%). RTs faster/slower than the overall subject mean minus/plus 2 SDs (4.01%) and error due to imprecise microphone recording (6.28%) were excluded from the analyses. There was no evidence of speed–accuracy trade-off ($r = 0.05$, $p > 0.8$), therefore we focused on RTs analyses. Mean correct RTs were submitted to a repeated-measures ANOVA with *Order* (object–number vs. number–object), *Object type* (graspable vs. ungraspable), *Object size* (small vs. large), and *Numerical magnitude* (small vs. large) as within-subjects factors. Fisher's LSD *post hoc* tests were also conducted on significant interactions.

The main effect of *Order*, $F(1,29) = 77.35$, $\text{MSE} = 20206.63$, $p < 0.001$, and of *Object type*, $F(1,29) = 15.74$, $\text{MSE} = 3138.92$, $p < 0.001$, were significant. RTs were faster for the object–number condition than for the number–object one (700 and 815 ms, respectively), and they were faster for graspable objects than for ungraspable ones (747 and 768 ms, respectively).

The interaction between *Order* and *Object type*, $F(1,29) = 7.73$, $\text{MSE} = 4668.80$, $p < 0.05$, was significant. *Post hoc* tests showed significantly faster RTs for graspable objects than for ungraspable ones only in the number–object condition (796 and 833 ms, $p < 0.001$, **Figure 2**). The interaction between *Object type* and *Object size*, $F(1,29) = 11.62$, $\text{MSE} = 2162.17$, $p < 0.05$, was significant. For graspable objects RTs were faster when the objects were large than small (740 and 755 ms, $p < 0.05$). The reverse was true for ungraspable objects: RTs were faster for small objects than large ones (760 and 775 ms, $p < 0.05$).

Furthermore, *Object size* interacted also with *Numerical magnitude*, $F(1,29) = 4.26$, $\text{MSE} = 3087.76$, $p < 0.05$. *Post hoc* test revealed that RTs were faster for smaller digits than for larger ones only when presented with large objects (748 and 767 ms, $p < 0.05$).

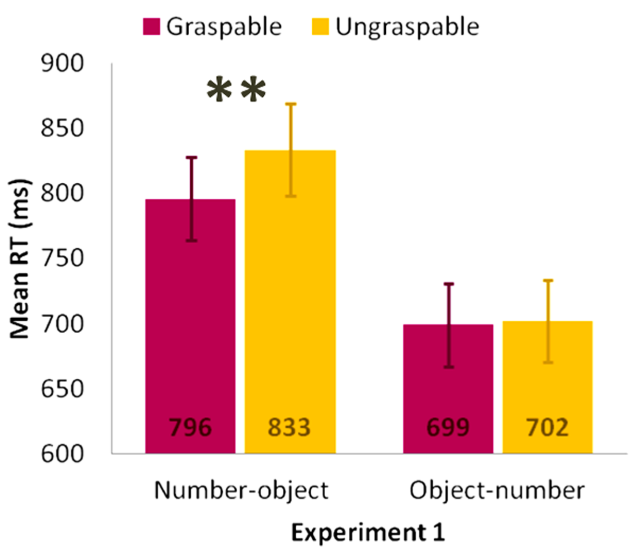

FIGURE 2 | Significant *Order* × *Object type* interaction for RTs in Experiment 1, values are in ms and bars are SEM. Significant comparisons are indicated with *(p < 0.05) or **(p < 0.01).

Finally, the significant interaction between *Order*, *Object type*, and *Numerical magnitude* factors, $F(1,29) = 4.49$, MSE = 2676.75, $p < 0.05$, revealed that affordance facilitated number processing (**Figure 3**). More specifically, in the number–object condition there was no significant difference between small and large numbers, neither when numbers were followed by a graspable object (801 and 791 ms, $ps > 0.3$), nor when they were followed by an ungraspable one (829 and 838, $ps > 0.3$). In the object–number condition, RTs were significantly faster for small compared to large numbers when preceded by a graspable object (685 and 713 ms, $p < 0.05$), but not when they were preceded by an ungraspable one (699 and 705 ms, $p > 0.5$). Again, there was no significant difference between the large number – graspable object association compared to the large number – ungraspable objects one ($p > 0.1$). The small number – graspable objects association was faster than the small number – ungraspable object one, although not significantly ($p > 0.1$).

No other effects or interactions were significant ($ps > 0.05$).

DISCUSSION

The main results of Experiment 1 showed that numerical processing is linked to object graspability. First, only graspable objects processing was speeded-up by the previous presentation of the numbers, indicating that numbers enhance graspable objects processing. Second, also graspability enhanced number processing. Indeed, the numerical magnitude effect (faster responses for smaller numbers than larger ones) emerged only after the presentation of graspable objects. It is worth noting that graspable and ungraspable objects generated different behavioral effects, suggesting that graspability was properly processed. In particular, results are in line with the view that graspable objects might be grounded in action (i.e., slower responses for graspable-small objects than large ones), as grasping a small object is a complex movement for a precise, functional grip usually requiring more time than a power grip (Bazzarin et al., 2007; Borghi et al., 2007a; Vainio et al., 2008; Ranzini et al., 2011).

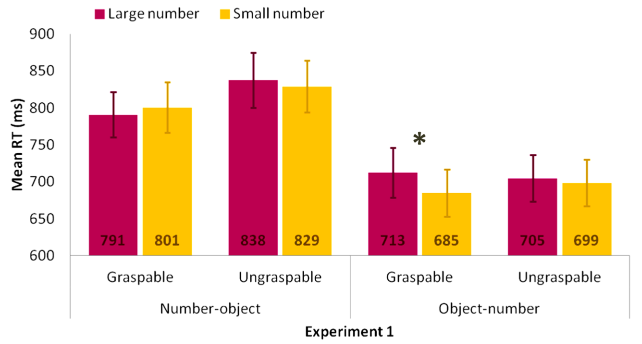

FIGURE 3 | Significant *Order* × *Object type* × *Numerical magnitude* interaction for RTs in Experiment 1, values are in millisecond and bars are SEM. Significant comparisons are indicated with *(p < 0.05) or **(p < 0.01).

EXPERIMENT 2

Experiment 1 extended previous results (Badets and Pesenti, 2010) demonstrating that not only the action perception, but also the object affordances affect number processing. In Experiment 2 we directly investigated the role of a hand action during the same task. Participants had to hold an object in their hands and keep it lifted from the table during the execution of the task of Experiment 1, so that the holding action was completely task-irrelevant. However, if similar mechanisms subtend number processing, object affordances, and action execution, we would expect the holding action to interfere with the processing of affordances and of numerical magnitude. Moreover, as previous studies have suggested that response modalities involving grasping (Anelli et al., 2010) or preliminary motor training (Borghi et al., 2007b: Experiment 2) enhanced information related to object manipulation, we expected that the holding action would enhance the sensitivity for the size of the observed graspable objects.

METHOD

Participants

Twenty undergraduate students (three males and 17 females; mean age: 20.2 years; all right-handed) from the University of Bologna took part in the Experiment 2 for course credits. As in Experiment 1, all participants had normal or corrected-to-normal vision, were naive as to the purpose of the experiment and gave written informed consent.

Apparatus, stimuli, and procedure

The apparatus was the same used in Experiment 1. However, in the present experiment participants were required to grasp and lift an object with both hands and continue to hold it lifted during the task. Participants could comfortably stay with their elbows on the table during the execution of the task, however they were required to keep the hand muscles in a tensed position in order to keep lifting the object from the table (at the height they were comfortable, and without interfering with the screen visibility). The object was a neutral-colored egg-shaped artifact, graspable with both hands by power grips at its central part (the body of the object was 13 cm × 6 cm), and graspable with both hands by precision grips at its extremities (extremities were 10 cm × 1 cm). Power or precision grip were counterbalanced between sessions and not considered as a factor[1]. The four-factors-of-interest were the same of Experiment 1: *Order* (object–number vs. number–object), *Object type* (graspable vs. ungraspable), *Object size* (small vs. large), and *Numerical magnitude* (small vs. large number). In order to reduce the number of trials, in Experiment 2 we presented six objects for each of the four categories (graspable-small objects, graspable-large objects, ungraspable-small objects, ungraspable-large objects), see **Table 2**. The objects could be small (mean pixel 85 × 148) or large (mean pixel 410 × 480). As in Experiment 1, there were eight different sessions, but each session consisted of one practice block of 12 trials and one experimental block of 24 trials. Overall the experiment consisted of 192 experimental trials and lasted about 45 min.

RESULTS

The data were trimmed according to the same criteria used for Experiment 1. The incorrect responses were removed from the analysis (2.9%, range 0–9%). RTs faster/slower than the overall subject mean minus/plus 2 SDs (3.72%) and error due to the microphone recording (2.86%) were excluded from the analyses. As in Experiment 1, there was no speed–accuracy trade-off ($r = 0.08$, $p > 0.7$), therefore we focused on RTs analyses. An ANOVA with the same factors as those of Experiment 1 was conducted.

The main effects of *Order*, $F(1,19) = 20.45$, MSE = 21795.36, $p < 0.001$, and of *Numerical magnitude*, $F(1,19) = 13.88$, MSE = 7459.50, $p < 0.001$, were significant. RTs were faster for the object–number condition than for the number–object one (685 and 760 ms, respectively), and they were faster for the small number condition than for the large number one (705 and 741 ms, respectively). Furthermore, the *Order* × *Object type* × *Object size* × *Numerical magnitude* interaction was significant, $F(1,19) = 5.49$, MSE = 660.46, $p < 0.05$. No other effects nor interactions were significant ($ps > 0.05$). To better understand this third-order interaction, separated analyses by levels of *Order* were performed. The main effect of *Numerical magnitude* was significant both for the object–number condition, $F(1,19) = 11.15$, MSE = 6716.11, $p < 0.05$ (small and large digits, respectively: 664 and 707 ms), and for the number–object one, $F(1,19) = 9.67$, MSE = 3407.64, $p < 0.05$ (small and large digits, respectively: 746 and 774 ms), revealing in both cases quicker responses for the small digits.

Crucially, the *Object type* × *Object size* × *Numerical magnitude* interaction was significant only for the object–number condition, $F(1,19) = 6.08$, MSE = 1284.16, $p < 0.05$, **Figure 4**. *Post hoc* tests revealed that the size of the object and the size of the number interacted differently for the graspable and ungraspable objects. On one hand, in the ungraspable-small object combination results showed a facilitation for the small numbers (647 ms) compared to the large ones (712 ms), $p < 0.001$. Similarly, when the object was ungraspable and large, RTs were faster when the following number was small (674 ms) than large (713 ms), $p < 0.001$. On the other hand, when the object is graspable and small, no difference was found for the small (668 ms) and large numbers (688 ms), $p = 0.10$. Differently, in the graspable-large object combination, RTs were faster for the small numbers (665 ms) than large one (714 ms), $p < 0.001$. In other words, in the object–number condition, the number magnitude effect was reduced when the object was graspable and small (RTs for large minus small number difference = 20 ms, **Figure 4**)

Table 2 | The 24 objects of Experiment 2.

Graspable objects		Ungraspable objects	
Small	**Large**	**Small**	**Large**
Almond	Ball	Atom	Bell
Clippers	Case	DNA	Bench
Match	Coconut	Exclamation mark	Bush
Nut	Courgette	Flame	Hedge
Pastry	Eggplant	Ink stain	Roadsign
Ticket	Vase	Question mark	Rock

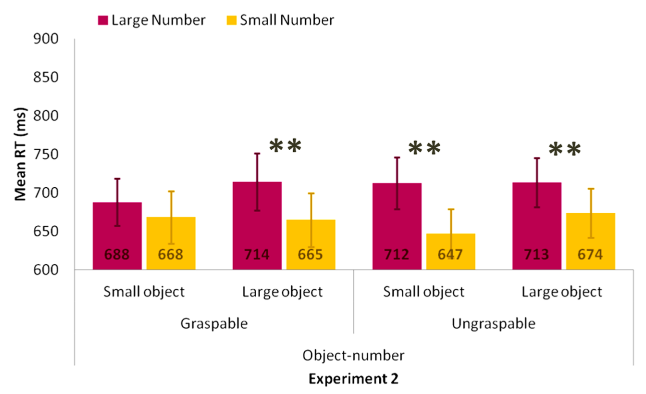

FIGURE 4 | Significant *Order* × *Object type* × *Object size* × *Numerical magnitude* interaction for RTs in the object–number condition of Experiment 2. Values are in millisecond and bars are SEM. Significant comparisons are indicated with *($p < 0.05$) or **($p < 0.01$).

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[1] Because it was not of our theoretical interest, analysis including *Grip* factor are not reported in the main text. However, since previous studies showed significant interactions between the type of grip and the numerical magnitude (e.g., Lindemann et al., 2007), we run the ANOVA with *Grip* (power vs. precision), *Order* (object–number vs. number–object), *Object type* (graspable vs. ungraspable), *Object size* (small vs. large) and *Numerical magnitude* (small vs. large) as *within*-subjects factors. The main effect of *Grip* was not significant, $F(1,19) = 0.233$, MSE = 75647.54, $p = 0.635$. No interactions with the *Grip* factor and both *Numerical magnitude* or *Object type* were significant. Interestingly, the *Oder* × *Object type* × *Object size* × *Numerical magnitude* interaction was significant, $F(1,19) = 8.66$, MSE = 1118.11, $p < 0.05$. Since the latter interaction resulted as significant, we believe that it is appropriate to not include the *Grip* factor in the analysis reported in the main text. Importantly, though, the mean RT values of the present analysis show a similar trend to that observed for the analysis reported in the main text. Therefore, we think that it indicates a convergence in the overall results and that the *Grip* factor did not interfere with our variables of interest.

compared to the other conditions (RTs for large minus small number differences range between 39 and 65 ms, **Figure 4**).

Comparison between Experiments 1 and 2

To statistically prove the difference between experiments in the numerical magnitude effects, a direct comparison of Experiments 1 and 2 was performed. An ANOVA with the main within-subject factors *Order*, *Object Type*, *Object Size*, *Numerical Magnitude*, and with *Experiment* (1, 2) as between subjects factor, was conducted. For simplicity, only the significant effects in which an interaction with the factor *Experiment* are reported here. Crucially, the interaction between *Numerical Magnitude* and *Experiment* was significant, $F(1,48) = 5.65$, MSE = 6547.69, $p < 0.05$, **Figure 5**, indicating that the numerical magnitude effect was enhanced in Experiment 2 compared to Experiment 1 (note that the main effect of *Numerical Magnitude* was also significant in this analysis, $F(1,48) = 14.32$, MSE = 6547.69, $p < 0.001$). Again, the interaction between *Order*, *Object Type*, *Numerical Magnitude*, and *Experiment* was significant, $F(1,48) = 7.41$, MSE = 2334.95, $p < 0.01$. Indeed, the magnitude effect was overall present in these conditions of Experiment 2, as suggested by the absence of an interaction between *Order* × *Object Type* × *Numerical Magnitude* in this experiment (see Results in Experiment 2). In contrast, in Experiment 1 the magnitude effect was significantly present only when a graspable object preceded the numbers presentation, as indicated by the significant triple interaction in this experiment (see Results in Experiment 1, **Figure 3**).

DISCUSSION

Results of Experiment 2 showed that the holding action interacted with the processing of the numerical magnitude, and interfered with the object–number relationship. Firstly, we found that holding the object in the hands enhanced overall number processing, as revealed by the significant main effect of numerical magnitude not present in Experiment 1. Secondly, we found that the holding action concurrent to the task interfered with the effect of the affordances on the processing of numbers, however enhancing the sensitivity for object size. Specifically, the numerical magnitude effect was disturbed only after the presentation of graspable-small objects.

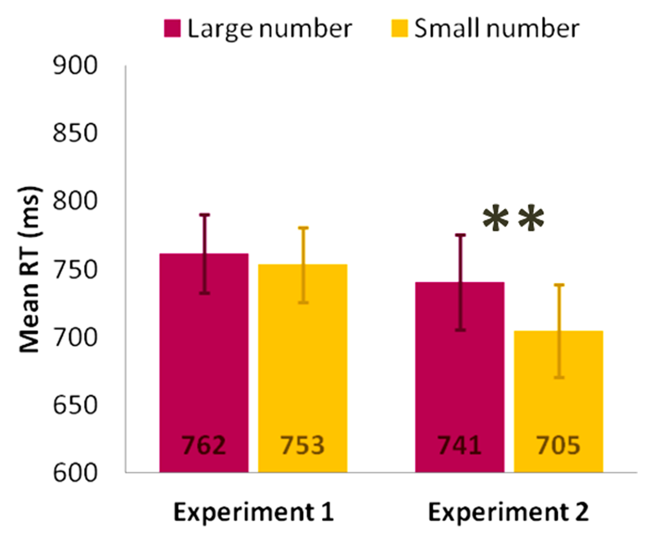

FIGURE 5 | Significant *Numerical Magnitude* × *Experiment interaction,* values are in millisecond and bars are SEM. Significant comparisons are indicated with *(p < 0.05) or **(p < 0.01).

GENERAL DISCUSSION

The present study aims at investigating the effects of objects affordances, i.e., objects possibilities for action (Gibson, 1979; Ellis and Tucker, 2000), on number processing. In two experiments, we adopted a parity judgment paradigm, where the numerical stimuli were preceded or followed by the presentation of an object, which could be graspable or ungraspable. The response to the numerical stimulus varied in function of the type of object. As previous studies suggested that numerical magnitude is grounded in action networks (e.g., Badets and Pesenti, 2010), we hypothesized that observing objects which activate grasping affordances may influence the processing of the numerical magnitude. Moreover, we were interested in investigating the link between the action network involved in object observation comparing a condition without (Experiment 1) or with (Experiment 2) the requirement of a task-irrelevant hand action (i.e., holding an object in the hands).

In Experiment 1, we observed that the numerical magnitude processing system had mechanisms in common with graspable objects. This was exploited by two major findings. Firstly, we found that responses to graspable objects compared to ungraspable ones were faster when numbers preceded the presentation of the object. A similar result was observed by Badets and Pesenti (2010), who showed that responses to biological hands were faster in the semantic-to-motor condition (i.e., when numbers preceded the presentation of the hand). While Badets and Pesenti (2010) found this effect with biological hands, which directly evoke motor information, the novelty here lies in finding this result when a graspable object was shown compared to an ungraspable one. This suggests that the simple presence of graspable objects activates motor information, probably through the mediation of the canonical neuron system. Secondly, and more crucially, we found that when graspable objects preceded the numerical stimuli there was a significant numerical magnitude effect not observed in the other conditions. It is worth noting that in this experiment, in line with a classical numerical magnitude effect, responses were overall quicker to small numbers than to large ones, even if this difference did not reach significance. This seems to suggest that activating action mechanisms, related to object grasping, enhances the sensitivity to numerical magnitude. Alternatively or in addition, in a motor account, as only small numbers should constitute an expectable outcome after the activation of grasping circuits by graspable objects (Badets and Pesenti, 2010), we predicted a facilitation for small numbers and/or an interference for large ones when preceded by graspable compared to ungraspable objects. This was exactly what we observed: responses to small numbers were overall quicker after graspable than ungraspable objects, and the opposite was true for large numbers, although both comparisons were not significant. In our opinion, the findings of Experiment 1 converge to support a sensory–motor interpretation of our results. Specifically, they suggest that number processing and object affordances involve interacting or overlapping mechanisms, and the anatomical organization of the numerical and of the grasping circuitries in the IPS supports this view. These findings add to the existing literature on number–action interactions, demonstrating that object affordances, similarly to action observation (Badets and Pesenti, 2010), modulate number processing. Importantly, the interaction we observed in Experiment 1 between the object type and the object size suggests that the graspable objects were processed at a motor level. For instance, the slower responses for graspable-small objects compared to graspable-large ones mirror the disparities between the time required to perform a precision grip when grasping small objects and the time required to perform a power grasp to large objects (Ehrsson et al., 2000; Borghi et al., 2007a).

Concerning results of Experiment 1, it remains to understand the role that objects size played in this experiment. A number of studies showed associations between numerical magnitude and other physical dimensions (e.g., Henik and Tzelgov, 1982). However, the main findings including number processing in Experiment 1 were affected in no way by the object size. On the other hand, we observed an unclear interaction between numerical magnitude and object size which was independent from other factors. To permit to motor associations to emerge irrespective of other perceptual factors, we presented small and large objects in different counterbalanced blocks, minimizing in this way possible perceptual effects of object size. Possibly, this manipulation interfered with a natural perceptual association between smallness or largeness, although we believe that this manipulation did in no case affect our main results related to the affordances.

In Experiment 2 we wanted to confirm that the effects observed in Experiment 1 were due to shared motor mechanisms belonging to both numbers and graspable objects. In fact, it is possible that, as no hand action was required during the Experiment 1, results could have alternative explanations, not necessarily involving sensory–motor systems. For this reason, in Experiment 2 we asked to another group of participants to hold an object in their hands during the execution of the same task, in order to explore the effects of the engagement of the motor system on object affordances and numerical magnitude. This manipulation was introduced in order to investigate effects of affordances on number processing, both when they were perceived through object observation and when they were experienced through object holding. We underline that – to the best of our knowledge – no previous studies have investigated the effects of a task-irrelevant holding action on the processing of numerical magnitude. Moreover, as previous studies have shown that motor action executions enhanced the sensitivity to the features of the objects related to their manipulability (Borghi et al., 2007b; Anelli et al., 2010), we expected here a contribution of object size on the effects related to numbers.

Firstly, we found that holding an object in the hands during a numerical task enhanced the sensitivity to numerical magnitude. Indeed, the classical numerical magnitude effect emerged overall, differently to what observed in Experiment 1. This confirmed that a hand action toward an object enhanced the sensitivity to target stimuli features (e.g., Anelli et al., 2010). However, interestingly, in this case this effect was found for numbers rather than for objects. In a neuro-anatomical perspective, this behavioral data go together with fMRI results showing that aIPS was more strongly activated during grasping execution than during the observation of 3D objects, although it was nonetheless activated during the latter case (Cavina-Pratesi et al., 2007). Thus, we can imagine that interactions between numbers and action-related mechanisms might be stronger in the case of greater activations of the IPS circuits.

The second result of Experiment 2 was that the effect of numerical magnitude was affected when numbers were preceded by a small graspable object. This finding leads to some main conclusions. Firstly, it provides further evidence for the view that numbers and graspable objects interact through action mechanisms. Secondly, it suggests that a crucial role in this interaction might be played by precision grip movements, as only small objects – which require precision grips – affected the sensitivity to numerical magnitude when the motor system had already been engaged. Importantly, some neuroimaging studies have suggested that the IPS can be primarily related to the precision grip (Ehrsson et al., 2001; Begliomini et al., 2007). Moreover, Valyear et al. (2007), in a study comparing tools with graspable or ungraspable objects, suggested that the activation in the left aIPS may reflect sensory–motor processes involved in the use of familiar tools, more than a general representation of grasping affordance. Taken together, these findings permit to speculate on the nature of the object–number interactions. Specifically, if the IPS is primarily responsible for the computation of small familiar objects, holding the object during the Experiment 2 might have disclosed a specific association between small objects and numbers. However, as we counterbalanced the kind of grip that participants used to hold the object, it is possible that this manipulation interfered with the effects related to the object size, leaving this hypothesis open for future studies.

In summary, this study provides evidence that number representations are grounded into perception–action systems, showing that both object affordances (Experiment 1) and task-irrelevant hand action (Experiment 2) enhanced the sensitivity to numerical magnitude. The novelty of the present study is at least twofold. First, these findings indicate that semantic numerical knowledge can emerge not only from the observation of biological grasping movements (Badets and Pesenti, 2010), but also from the observation of object affordances. Importantly, the relationship between the number processing and the grasping system was found in a task that did not directly link graspability with numerical magnitude (i.e., parity judgment task). Second, to our knowledge this is the first study in which the relationship between number processing and affordances is explored asking participants to execute a task-irrelevant hand action during the experiment. The relation between numbers and size when it is mediated by objects, in particular by graspable objects, remains however to be deeper explored. Differently to what observed by previous behavioral (Henik and Tzelgov, 1982) and neuroimaging studies (Fias et al., 2003; Pinel et al., 2004; Cohen Kadosh et al., 2005), the present study suggests that the interaction between size and numerical magnitude, when mediated by object affordances, might be more complex than a classical association of smallness or largeness. It is possible that tools-driven precision grip mechanisms might be principally related to the processing of the numerical magnitude.

In conclusion, embodied cognition theories claim that abstract and concrete concepts are grounded in perception–action systems (e.g., Glenberg, 1997; Barsalou, 1999, 2008; Gallese and Lakoff, 2005). The results of this study support this view, by showing that objects, either observed (Experiment 1) or motorily experienced (Experiment 2), evoke grasping affordances that shape the processing of numerical magnitude. The strict linkage we found between number processing and object perception and action can be accounted by ideomotor theories. In particular, it is compatible with the theory of event coding (TEC; Hommel et al., 2001), according to which perceived events, i.e., perceptions, and events to be produced, i.e., actions, are represented by the same "event codes". Consequently, perception and action systems rely on the same representational format as they both are events in the environment. In this case, numbers and objects would rely on both perception and action, which are encoded in the same format or file.

Further studies will need to clarify to which extent the developing of the numerical knowledge on specific cultural habits (i.e., finger counting) accounts for action-based numerical magnitude processes in adulthood, and how exactly neural brain networks work to merge semantic aspects of numerical cognition to action.

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Developmental changes in the profiles of dyscalculia: an explanation based on a double exact-and-approximate number representation model

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Studies on developmental dyscalculia (DD) have tried to identify a basic numerical deficit that could account for this specific learning disability. The first proposition was that the number magnitude representation of these children was impaired. However, Rousselle and Noël (2007) brought data showing that this was not the case but rather that these children were impaired when processing the magnitude of symbolic numbers only. Since then, incongruent results have been published. In this paper, we will propose a developmental perspective on this issue. We will argue that the first deficit shown in DD regards the building of an exact representation of numerical value, thanks to the learning of symbolic numbers, and that the reduced acuity of the approximate number magnitude system appears only later and is secondary to the first deficit.

Keywords: developmental dyscalculia, number processing, approximate number representation, exact number representation

Developmental dyscalculia (DD) is a persistent and specific disorder of the numerical development and mathematical learning. In the recent years, several authors have proposed that DD arises from a fundamental impairment in the representation of number magnitudes (e.g., Butterworth, 1999, 2005; Wilson and Dehaene, 2007). In this paper, we will argue that the first deficit shown in DD does not support the hypothesis of an impairment at that level. Rather, we will argue that the first deficits of DD regards the construction of an exact representation of numerical value, that builds on the acquisition of symbolic number meaning[1]. The reduced acuity of the approximate number magnitude system would only appear later and would be secondary to the first deficit.

According to what we will call *the simple story*, babies are born with an innate analog magnitude system specifically tuned to numerical information (Xu and Spelke, 2000; Lipton and Spelke, 2003, 2004; Xu, 2003; Feigenson et al., 2004; Xu et al., 2005). This system yields approximate, noisy representations and is thus called the *approximate number system* or ANS. Throughout the development, the acuity of that system increases (Halberda and Feigenson, 2008). When the child learns the number words in the counting routine, these symbols take their meaning from the connections they establish with this ANS (Dehaene, 1992; Gallistel and Gelman, 1992; Dehaene and Cohen, 1995, 1997). Finally, this ANS would also be crucial for more advanced numerical learning as individual differences in the acuity of that representation correlate with mathematics achievement (Halberda et al., 2008). Accordingly, some researchers have argued that DD could result from a core dysfunction of that representation (Butterworth, 1999, 2005; Landerl et al., 2004; Wilson and Dehaene, 2007). Indeed, several authors found that, when comparing sets of dots, DD children showed less sensitivity to numerical differences than control children, thus showing a reduced number acuity (Piazza et al., 2010; Mazzocco et al., 2011). Similarly, Mussolin et al. (2010) observed that DD children were slower and less accurate than control children when comparing small and close numerosities. Finally, using a free estimation production task with completely non-symbolic input and output, Mejias et al. (in press) observed that the estimates produced by DD children were less precise and more variable that those of typically achieving children (see also Mazzocco et al., 2011 for similar observations). All these data thus support the hypothesis of a deficient ANS in DDs.

However, a number of researches brought data that are inconsistent with this view. First, in unselected populations, performance in the comparison of two sets of dots failed to account for individual difference in mathematics (Holloway and Ansari, 2009; Mundy and Gilmore, 2009). Second, when comparing the magnitude of two sets of dots, a series of studies (Rousselle and Noël, 2007; Iuculano et al., 2008; Landerl and Kölle, 2009; De Smedt and Gilmore, 2011) failed to find any difference between the performance of DD and control children. However, in all these studies, DD children displayed significant impairment in Arabic number comparison and calculation. Accordingly, Rousselle and Noël (2007) proposed that the central deficit in DD children would not be a defect of the ANS itself but rather in accessing the numerical magnitude information conveyed by symbols such as Arabic numbers or number words.

How can we account for this contradictory pattern of results? We could first consider the type of measure used. For instance,

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[1] In this paper, the terms "symbolic numbers" must be understood as every symbols that bear a precise cardinal meaning and that are part of an ordered sequence. In typical development, the first symbols referring to a precise numerosity are certainly verbal number words but in other culture, it could be body part counting for example.

Piazza et al. (2010) and Mazzocco et al. (2011) measured the acuity of the ANS by calculating the index *w*. Such a method was not used by the other authors. However, among those who measured a distance effect, another indicator of the precision of the ANS, some found significant difference between DD and control children (e.g., Price et al., 2007; Mussolin et al., 2010) and some did not (e.g., Landerl and Kölle, 2009; De Smedt and Gilmore, 2011). If we list all the studies that have compared DD and control children's ability to process the magnitude of non-symbolic (i.e., dot collections) or symbolic numbers (Arabic digits or number words) and order them according to the age of the children tested (see **Table 1**), a clear picture emerges. First, at all ages, DD children perform significantly lower than controls in the magnitude comparison tasks using symbolic numbers. Second, for tasks using non-symbolic numbers, a dissociation appears between the studies which tested younger (6–9 years old) versus older children (10 years old and above): only the latter showed some significant difference[2]. Thus, the first deficit seen in DD children is specific to the magnitude processing of symbolic numbers. Dyscalculia children's deficit in processing non-symbolic number magnitude only appears later, on a second time.

Given the changing profile of DD according to their age, a developmental perspective must be adopted. However, considering this picture, it should be acknowledged that *the simple story* can not easily explain why DD children would have a first difficulty with number symbols and only later with the ANS, especially if we consider than the meaning of number symbols is learned through the mapping with the ANS. At this point, it is thus necessary to consider other theoretical perspectives.

More and more recent developmental data support the idea that the meaning of number words is not gained through the simple mapping between these number words and the ANS. First, if the child simply has to map number symbols to the ANS, why would it take so long before he/she understands the meaning of the number words? At least a year elapses between the time a child is able to recite the counting sequence and the moment he/she comes to understand the cardinal value of the verbal numerals in the sequence (as demonstrated by succeeding at tasks such as "What is on this card?" or "Give me *n* items"; Wynn, 1992). Second, young children who do not yet understand the precise meaning of the number words in their counting sequence do not show the typical characteristics of ANS when required to estimate the number of items in a set (Lipton and Spelke, 2005; Le Corre and Carey, 2007).

For these reasons, another set of theories has been put forward which argue that the learning of symbolic numbers would lead to the emergence of a new numerical representation system in human ontogeny (see Carey, 2001, 2004; Wiese, 2003b, 2007; Noël et al., 2008). Endowed with a semantic content based on the ordinal information enclosed in the symbol sequence, this new representation would allow representing exact numerical value, contrary to the ANS which is only an approximate representation of number magnitude.

Carey's (2001, 2004, 2009) developmental model perfectly illustrates this standpoint. She proposes that representations of natural numbers are first built on a "parallel individuation" system allowing babies to keep track of the items in a small set through mental models which encode their spatio-temporal properties (Kahneman et al., 1992; Trick and Pylyshyn, 1994; Simon, 1997). Indeed, contrarily to the ANS, the parallel individuation system provides an exact, although implicit, representation of small numerosities and, by creating a mental model for each new element, provides a natural representation of the operation of "adding one" to an array. The capacity to represent ordered relations, and the sensitivity to syntactico-semantic markers of quantification present in language, could also play a significant role in this developmental step (see also Wiese, 2003a,b; Sarnecka et al., 2007). All these tools would help children gradually learn the meaning of the number words *one*, then a few months later *two*, then again a few months later *three*, and then *four*. As this parallel individuation system is very limited and only allows the child to track 3 or 4 items in parallel, another processing is required for the next developmental step.

At this point, the child has to discover that the cardinal value of a number word is determined by its order on the list, and that successive numbers are related by the function "+1": For any known number n in the list, the value of the next number is $n + 1$. This successor function is probably worked out by induction on the basis of the child's knowledge of the cardinal meaning of *one, two, three,* and *four*. Sarnecka and Carey (2008) have shown that this conceptual jump is, at least, a two-stage process. First, children understand that adding one item to a set leads to a cardinal which is labeled by a word further away in the counting list than the word denoting the initial cardinal. Second, children understand that adding one item to a set leads to a cardinal labeled by the word just after the one used to tag the initial cardinal. At this point, children master the successor function and have discovered how verbal numerals represent the natural numbers.

In Carey's view, it is only after children have created this new representation of exact numbers that they start to map it with the ANS (see Le Corre and Carey, 2007) and thus establish connections between the old, approximate representation of number

Table 1 | Comparison of the performance of DD and Control children in the symbolic or non-symbolic number comparison.

References	Age (years old)	Symbolic	Non-symbolic
De Smedt and Gilmore (2011)	6	DD < C	DD = C
Rousselle and Noël (2007)	7	DD < C	DD = C
Landerl et al. (2004)	8–9	DD < C	–
Iuculano et al. (2008)	8–9	DD < C	DD = C
Landerl and Kölle (2009)	8–9–10	DD < C	DD = C
Landerl et al. (2009)	8–9–10	DD < C	DD < C
Piazza et al. (2010)	10	–	DD < C
Mussolin et al. (2010)	10–11	DD < C	DD < C
Price et al. (2007)	12	–	DD < C
Mazzocco et al. (2011)	14	–	DD < C

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[2] Let us however note a difference in the profiles obtained by Landerl et al. (2009) and by Landerl and Kölle (2009). Although they used the same tasks and the same age range for participants, only the first one showed slower RTs in the non-symbolic magnitude comparison task. The only difference between the studies is that the cutoff criteria to define MLD is 1 SD below the mean in the first one and 1.5 SD below the mean in the second one.

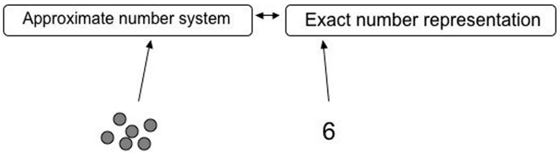

FIGURE 1 | A two semantic number representation model with an approximate representation for non-symbolic numbers and an exact representation for symbolic numbers.

magnitude and the new, exact representation of natural numbers (see **Figure 1**).

This distinction between an approximate and an exact representation is also consistent with cross-cultural evidence showing that adults leaving in cultures with very limited number lexicon and no counting system are unable to develop an exact representation of numbers beyond 3 or 4, although their ANS is quite normal (Gordon, 2004; Pica et al., 2004). Similarly, deaf adults leaving in numerate communities who have developed their own signs for numbers but not embedded in a counting system do not develop representations of large exact numerosities (Spaepen et al., 2011). In summary, although we share an ANS with animals, it is only if we have the chance to learn a number system based on the successor function and embedded in a counting process that we can develop an exact representation of large numbers which is the basis of exact mathematics.

How can this developmental perspective shed light on the data of DD? As we saw, the first difficulties seen in DD children concern the processing of symbolic number magnitude. Accordingly, we propose that the first difficulty of DD children is to develop an exact representation of natural numbers. As for the first numbers, this representation is assumed to build on the parallel individuation system, DD children's difficulty to elaborate an exact numerical representation could originate from the limitation of this parallel tracking system, as manifested by the reduction of the subitizing range in children with DD (see Koontz and Berch, 1996; Schleifer and Landerl, 2011). But this initial limitation is probably not the only difficulty they would encounter in constructing an exact numerical representation. Later, the induction process needed to discover the successor function might also be impaired in DD children.

In Carey's (2004, 2009) model, once the child has developed an exact representation of natural numbers, he/she starts to connect it with the ANS. Because the representation of natural numbers is precise, some authors have assumed that its mapping onto the ANS would increase the precision of that intrinsically approximate system (see Halberda et al., 2008; Piazza et al., 2010). Indeed, change in number acuity are seen throughout the child's development (going from a $w = 0.525$ at age 3 to a $w = 0.179$ at age 6) up to adulthood ($w = 0.108$, Halberda and Feigenson, 2008). Of course, these changes might be due to natural brain maturation but concurrently, they might be stimulated by the manipulation, processing, and calculation of exact numbers. In the same way as color names in language defines category boundaries which influence color perception (Regier and Kay, 2009), the existence of number words referring to exact numerosities could in turn shape the perceived boundaries between numerosities at the non-symbolic level. In fact, the same kind of reciprocal influence has long been recognized in reading development: phonological abilities facilitate the development of reading but reading in turn improves phonological sensitivity as well (Perfetti et al., 1987; Bentin and Leshem, 1993; Burgess and Lonigan, 1998).

Such a hypothesis could explain why an initial difficulty with symbolic numbers and the manipulation of exact number processing would prevent DD children from refining their ANS in the same way as typically developing children do. This inefficient refinement would predict a slower growth of number acuity in DD children. This delayed maturation of number acuity would lead to increasing difference in number acuity between DD and control children over development. Thus, while only small and non-significant differences between DD and control children are measured in tasks tapping the precision of the ANS in young populations, larger and significant differences are reported in populations of older children.

To sum up, *the simple story* fails to give a plausible account for the developmental trajectory of the basic deficits actually reported in DD children. Here we argue that developmental theories assuming the construction of an exact representation of symbolic numbers (based on the ordinal properties of numbers in the counting sequence) offer a more powerful explanation for the pattern of results actually depicted in the literature. Considering the developmental course of DD children's impairments, we hypothesize that their first deficit, manifested in symbolic number processing tasks, would result from a basic dysfunction in the building process of this exact representation of symbolic numbers. Appearing later, the reduced acuity of the ANS would be the consequence, rather than the cause, of this first deficit.

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Malleability of the approximate number system: effects of feedback and training

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Prior research demonstrates that animals and humans share an approximate number system (ANS), characterized by ratio dependence and that the precision of this system increases substantially over human development. The goal of the present research was to investigate the malleability of the ANS (as measured by Weber fraction) in adult subjects in response to feedback and to explore the relationship between ANS acuity and acuity on another magnitude comparison task. We tested each of 20 subjects over six 1-h sessions. The main findings were that (a) Weber fractions rapidly decreased when trial-by-trial feedback was introduced in the second session and remained stable over continued training, (b) Weber fractions remained steady when trial-by-trial feedback was removed in session 6, (c) Weber fractions from the number comparison task were positively correlated with Weber fractions from a line length comparison task, (d) improvement in Weber fractions in response to feedback for the number task did not transfer to the line length task, (e) finally, the precision of the ANS was positively correlated with math, but not verbal, standardized aptitude scores. Potential neural correlates of the perceptual information and decision processes are considered, and predictions regarding the neural correlates of ANS malleability are discussed.

Keywords: numerosity, numerical, analog magnitudes, estimation, perceptual learning, approximate number system

INTRODUCTION

Mathematics is a uniquely human domain because it requires symbolic manipulation and an explicit understanding of the operations that allow calculation. However, in addition to a symbolic number capacity, adult humans also have an approximate number sense that allows us to estimate quantity without the use of symbols or language. Unlike precise symbolic representations of individual numbers, the approximate number system (ANS) encodes numerosities in a fuzzy fashion. A confluence of evidence suggests that the ANS emerges early in infancy and is shared by non-human animals (for reviews, see Dehaene, 1997; Feigenson et al., 2004). One basic feature of the ANS is that it follows Weber's law; the discriminability of two numerosities varies as a function of the ratio between them.

During the course of normal human development the ANS becomes more precise. Convergent evidence from multiple behavioral procedures demonstrates that while 6-month-old human infants require a 1:2 ratio to discriminate large numerosities, by 9-month they are able to discriminate a 2:3 ratio (e.g., Lipton and Spelke, 2004; Libertus and Brannon, 2010). Furthermore, cross-sectional studies that model Weber fraction (w) with explicit choice tasks indicate that the acuity of the ANS continues to increase from age 3 into adolescence (Halberda and Feigenson, 2008; see Piazza and Izard, 2009 for meta-analysis). At each age, however, and into adulthood there exists a large amount of inter-individual variability in w. Not surprisingly, an easy numerical discrimination for one person may be difficult for another.

One dominant theory is that the ANS serves as a foundation for symbolic mathematics (e.g., Dehaene, 1997; Wynn, 1998). Psychophysical markers such as the symbolic distance effect indicate that mathematical symbols are mapped onto analog magnitudes (Moyer and Landauer, 1967). Brain-imaging data indicate that symbolic calculations often activate the same brain areas involved in approximate estimation implying that the ANS is recruited during calculation (Fias et al., 2003; Venkatraman et al., 2005; Holloway et al., 2010). Only recently, however, has evidence emerged that individual differences in w are correlated with symbolic mathematical abilities (Halberda et al., 2008; Gilmore et al., 2010; Lyons and Beilock, 2011). These studies show that children and adults with higher ANS acuity (i.e., lower w) perform better in basic arithmetic and on standardized math tests. Furthermore, ANS acuity in preschoolers with no formal mathematics training correlates with later symbolic math performance, implying that ANS acuity may play a causal role in the development of higher math skills (Mazzocco et al., 2011b). Other evidence for the relationship between symbolic mathematics and number sense comes from atypically developing children. Developmental dyscalculia is a specific learning deficit in mathematics, and there is evidence that some dyscalculic children have severely impaired ANS acuity (Piazza et al., 2010; Mazzocco et al., 2011a). In addition, attempts to improve mathematical performance in dyscalculics that have centered on strengthening the connection between symbolic number representations and non-verbal numerosity representations (arrays of dots) have met with some success (Wilson et al., 2006b; Kucian et al., 2011).

The fact that symbolic math ability and the ANS are correlated throughout childhood raises the exciting possibility that honing the ANS could have lasting effects on symbolic mathematics. If so, even before children learn the meaning of number words interventions that increase ANS acuity may produce increases in math aptitude. The idea that ANS acuity might serve a foundational role in developing mathematical achievement, however, cannot be addressed without a better characterization of the ANS. For example, how reliable are measures of ANS acuity and can ANS acuity be improved with extended training?

Another important question is how the ANS relates to the perception and discrimination of other magnitudes. Walsh (2003) proposed a theory of magnitude (ATOM), which asserts that time, space, and number are all processed by a common analog magnitude system that depends on common parietal brain systems (see also Meck and Church, 1983; Cantlon et al., 2009). A prediction of ATOM is that individual variability in the ANS should be systematically related to precision in other magnitude judgments (e.g., temporal or size-based). A large literature addresses these questions in humans and animals using interference paradigms, transfer of learning tasks, and neuroimaging methods (for reviews, see Hubbard et al., 2005; Bueti and Walsh, 2009). Positive evidence from any of these sources could reflect a strong version of ATOM whereby two or more magnitudes are represented by a single common neural currency or a weaker version where different magnitudes share some common cognitive algorithms such as a comparison process (Cantlon et al., 2009).

We explored the malleability of ANS acuity by testing whether a simple training procedure in which we provided extended training over six sessions would improve ANS acuity. We also tested a prediction of ATOM by looking for correlations in Weber fractions derived from the numerosity comparison and those derived from a similar line length comparison task. In addition, our training paradigm allowed us to test a prediction of the strong version of ATOM by assessing whether improvements in the acuity of the ANS would transfer to line length comparison. We reasoned that if number and line length were represented using the same underlying representation (strong hypothesis), that any improvement in the number task would lead to an improvement in the line length task. If, however, we saw an improvement in ANS precision that did not transfer to the line length comparison we could conclude that the representations were not entirely overlapping, and more specifically the magnitude representations did not overlap on the level at which improvement occurred.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 20 adults (mean = 21.18 years, range 18.19–30.15 years) recruited from the Duke University community. Eleven of the 20 participants were female. One additional participant was excluded because she did not receive feedback during the second session due to experimenter error. All participants gave written informed consent in accordance with a Duke IRB approved protocol.

DESIGN

Each participant completed six sessions within 2 weeks. On session 1, participants performed the numerosity comparison task and the line length comparison task and did not receive any trial-by-trial feedback. On sessions 2–5, participants performed only the numerosity task and received trial-by-trial feedback. On session 6, participants performed the numerosity and line length tasks without trial-by-trial feedback. Each of the six sessions of the numerosity task contained six 108 trial blocks for a total of 648 trials per session. The two line length sessions each contained two 108 trial blocks for a total of 216 trials per session. In the final session participants self-reported their verbal and math SAT or GRE scores and these scores were later confirmed for 15/20 participants.

To motivate the participants to stay engaged in the task they were compensated based on performance. Each participant earned 0.0125 USD per correct answer in the numerosity task and 0.0375 USD per correct answer in the line length task. These performance bonuses were added to a baseline rate of 7.50 USD for sessions 1 and 6 and 5 USD for sessions 2–5. To motivate participants to complete the study they were given an additional 50 USD for completing all six sessions within a 2-week period.

TASKS

The numerosity comparison task

On each trial participants were presented with an array of intermixed black and white dots on a gray background for 200 ms. Half the participants were instructed to indicate whether there were more black dots or white dots, and the other half were instructed to indicate whether there were fewer black dots or white dots. Participants responded by pressing a black or white button on the keyboard, and the side of the response keys was counterbalanced across subjects. Although the stimuli were presented for only 200 ms, participants were allowed as long as they needed to respond and were encouraged to take their time and to be as accurate as possible. In the feedback sessions, a green or red screen lasting 1500 ms indicated a correct or incorrect choice respectively. The feedback screen was followed by a gray preparatory screen (1500 ms). In the no-feedback sessions, any response resulted in a blue screen (1500 ms) followed by a gray preparatory screen (1500 ms). Participants were given a break between each 108 trial block and were also allowed to pause the experiment at any time.

The line length comparison task

The structure was similar to the numerosity task, however, subjects were presented with a white and a black horizontal line and were required to indicate which was longer (or for half the subjects which was shorter) by pressing a black or white key. The line length comparison task was never administered with feedback, and it was only completed on sessions 1 and 6.

STIMULI AND APPARATUS

Each numerical stimulus consisted of an array of intermixed white and black dots (**Figure 1**). We tested six ratios of dots: 1:2, 2:3,

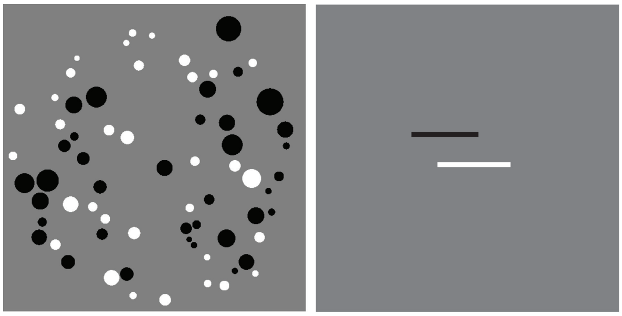

FIGURE 1 | Example stimuli from the numerical (left) and line length (right) tasks. The numerical stimulus has 33 white dots and 36 black dots and is an example of an 11:12 ratio. The black line in the line length stimulus is smaller than the white line by a factor of 11:12.

3:4, 5:6, 7:8, and 11:12. Absolute numerosity was roughly equated across the ratios, and the total number of dots within an array varied from 20 to 75. To ensure that subjects used numerosity and not surface area to complete the task on 1/3 of trials the total surface area of the array with fewer dots was smaller than the total surface area of the more numerous dots, on 1/3 of trials area was equal, and on 1/3 total surface area of the fewer dots was larger than the surface area of the more numerous dots. Similarly, to prevent subjects from using the size of the individual dots, on 1/3 of trials the average dot size of the fewer dots was smaller than the average dot size of the more numerous dots, and on 2/3 of trials the more numerous dots were smaller. The dots were drawn within a circle with a radius of 300 pixels.

The line stimuli consisted of one black and one white horizontal bar positioned at a constant vertical position (counterbalanced for which color was on top), but jittered horizontally from trial to trial (**Figure 1**). The same six ratios were used for line lengths and numerosities. The length of the bars varied from 64 to 384 pixels.

All stimuli were generated offline using custom MATLAB (MathWorks) scripts, and were presented using Psychophysics Toolbox Version 3 for MATLAB. Stimuli were presented and data collected on either a Dell Inspiron 530S or a Dell Optiplex 330. Participants made their response on a standard keyboard. Small stickers were used to denote the "black" and "white" response keys.

MODELING

For the purpose of modeling we assumed a linear internal representation of number with scalar variability following Pica et al. (2004) and Halberda et al. (2008). The error rate in our task is given by

$$\text{Error rate} = \frac{1}{2} \cdot \operatorname{erfc}\left(\frac{n_1 - n_2}{\sqrt{2} \cdot w \cdot \sqrt{n_1^2 + n_2^2}}\right) \tag{1}$$

Where n_1 is the numerosity of the larger set, n_2 is the numerosity of the smaller set, w is the measure of variance in the internal representation, and erfc is the complementary error function. We generated global estimates of w for each participant as well as session by session estimates of w for each participant by fitting this model to our data (Pica et al., 2004). **Figure 2** shows one participant's accuracy across different ratios and the model fit.

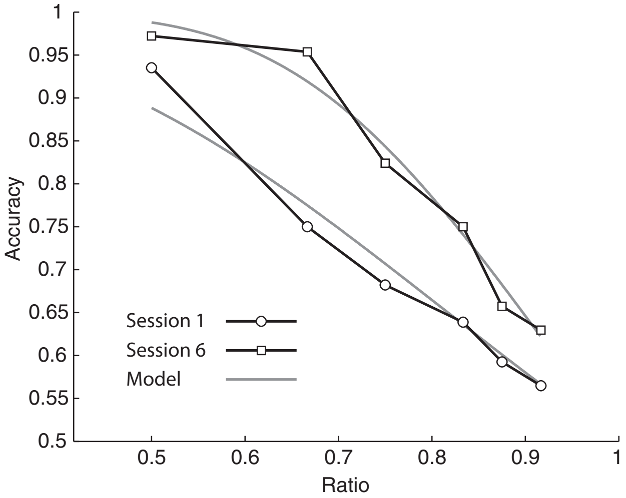

FIGURE 2 | Data collected from a single participant showing improvement in number acuity between session 1 (circles) and session 6 (squares). Gray lines show model predictions for the best fit w for session 1 ($w = 0.37$) and session 6 ($w = 0.20$). The improvement in w was typical of our sample.

SURFACE AREA EFFECT INDEX

As described above we controlled for surface area by using three randomly intermixed trial types. To assess the role of surface area on performance we calculated a surface area effect index by taking the absolute value of the difference between the accuracy on the trials where the smaller number of dots had fewer pixels (congruent) and the accuracy on the trials where the smaller number of dots had more pixels (incongruent). We also calculated a non-rectified surface area effect index by computing the difference between congruent and incongruent trials, but not taking the absolute value. This measure allowed us to assess whether the population as a whole had a bias toward congruent or incongruent trials before and after training.

TREATMENT OF OUTLIERS

Three of our participants (1, 5, and 16) returned w scores that were greater than 3 standard deviations above the mean (1.49, 1.23, and 1.36 respectively) for one of the six number sessions. On the other five sessions, these subjects' w values were within the same range as the other participants. We included these participants in our main analyses, but also reran the statistics excluding these three subjects to confirm the robustness of our findings. Unless otherwise noted, all tests reported as significant were also significant without outliers at $p < 0.05$, and tests reported as non-significant were also not significant without outliers at $p > 0.1$.

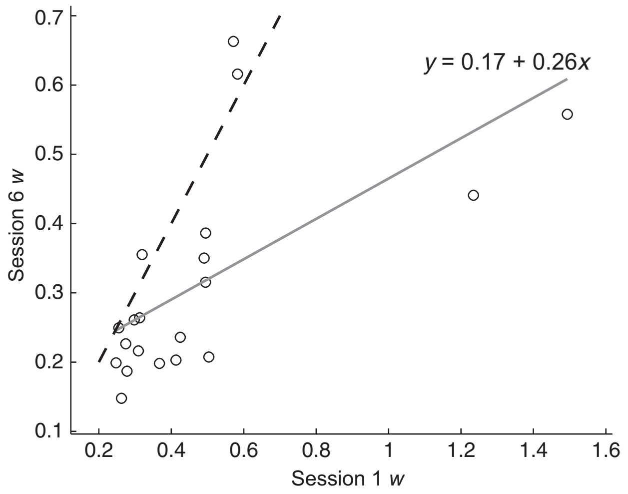

FIGURE 3 | Numerosity *w* scores calculated from session 6 plotted against numerosity *w* scores calculated from session 1. The dashed line shows equality. Participants below the equality line showed improvement in ANS acuity between sessions 1 and 6. The solid gray line is the best fit to the data and the equation shows the intercept and slope ($r^2 = 0.40$, $p < 0.005$).

RESULTS

There was strong ratio dependence in accuracy ($b = -0.77$, $p \ll 0.0001$)[1] and response time ($b = 0.53$, $p \ll 0.0001$) for the numerosity comparison task. The mean *w* for the sample was 0.33 with a standard deviation of 0.15. Within session reliability was computed by correlating split-halves of our six blocks and correcting for test length using the Spearman–Brown formula. Reliability was good, ranging from 0.83 to 0.94 over the six sessions. Our multi-session training procedure allowed us to further examine test–retest reliability across the 6 days of the study. **Figure 3** shows the strong positive correlation between *w* scores computed from the first session and last session.

To determine if *w* scores improved (decreased) with training we calculated *w* scores for each participant for each session. We then fit a logarithmic regression model to individual *w* scores with regressors for session number and participant (**Figure 4A**). The model accurately predicted *w* scores ($R^2 = 0.72$, $p \ll 0.0001$), and we found that *w* scores improved with training ($b = -0.047$, $p < 0.005$). However, the improvement in *w* scores occurred within the second session (the first session with feedback) and remained stable during the rest of training. Session 1 *w* scores were significantly higher than session 2 *w* scores (paired *t*-test, $p < 0.005$) and were also higher than session 6 *w* scores (paired *t*-test, $p < 0.01$). A logarithmic regression model applied to the session 2 through session 6 data showed no effect of session on *w* ($b = 0.008$, $p = 0.65$) demonstrating that the improvement in *w* was accomplished within the first session of trial-by-trial feedback and did not continue with extended training. **Figure 2** shows the accuracy data and model fit of a single participant for sessions 1 and 6. The improvement in *w* was typical of our sample.

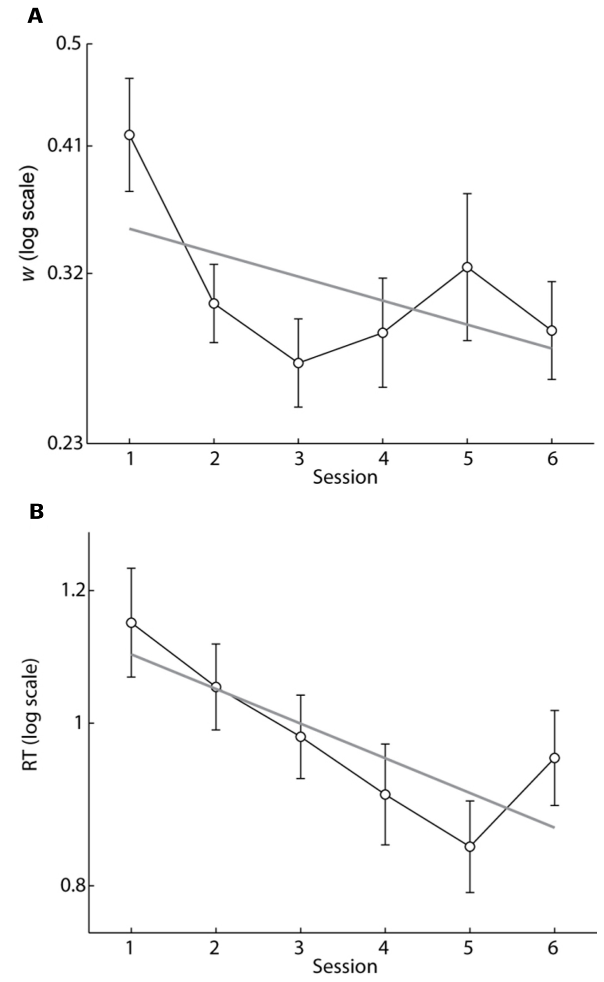

FIGURE 4 | (A) Mean *w* scores as a function of session number. Gray line is the best fit regression line to log(*w*) ($b = -0.047$, $p < 0.005$) accounting for repeated measures. Note the rapid decrease in *w* between sessions 1 and 2 where trial-by-trial feedback was introduced. Acuity did not improve further after session 2, but was sustained after feedback was removed on session 6. **(B)** Mean of the median RT for correct responses as a function of session number. Gray line is the best fit regression line to log(RT) ($b = -0.048$, $p \ll 0.0001$) accounting for repeated measures. RT continued to decrease with further training. Error bars indicate SEMs.

To determine if response time decreased with training we fit a logarithmic regression model with regressors for session number and participant to the median correct RT calculated for each subject for each session (**Figure 4B**). The model accurately predicted RT ($R^2 = 0.83$, $p \ll 0.0001$), and RT decreased with training ($b = -0.048$, $p \ll 0.0001$). Unlike *w*, however, RT continued to decrease from session 2 to 6 ($b = -0.035$, $p < 0.0001$). RT rebounded slightly on session 6 when feedback was removed. Nevertheless RT during session 6 was significantly lower than on session 1 indicating that the improvement was retained in the absence of feedback (paired *t*-test, $p < 0.005$).

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[1] There was no difference in *w* scores for subjects instructed to indicate the greater versus the fewer number of dots (*t*-test, $p = 0.62$) thus all analyses are collapsed across these two groups.

To measure the effect of cumulative surface area on participants' numerical estimation over training a surface area effect index was calculated by taking the absolute value of the difference between the accuracy on trials where the smaller number of dots had fewer pixels (congruent trials) and the accuracy on trials where the smaller number of dots had more pixels (incongruent trials). A linear regression accounting for repeated measures was then fit to the surface area index ($R^2 = 0.49$, $p \ll 0.0001$). The surface area effect index significantly decreased over sessions ($b = -0.02$, $p < 0.005$; **Figure 5**), indicating that at least part of the improvement in the numerosity task was due to a decrease in reliance on surface area as a cue for number. There was, however, variability across participants in the degree to which surface area affected numerosity judgments and also in the direction of this influence. During the first session most participants performed better on area congruent than on area incongruent trials. The mean non-rectified surface area effect index was significantly positive (mean = 0.24, SD = 0.27; *t*-test, $p < 0.001$), indicating higher accuracy on congruent trials. However, by the last session participants performed equally well on both types of trials (mean = −0.07, SD = 0.22; *t*-test, $p = 0.17$). Surprisingly, when outliers were removed from this analysis the non-rectified surface area index was slightly negative indicating that subjects performed better on incongruent trials by the last session (mean = −0.09, SD = 0.16; *t*-test, $p < 0.05$).

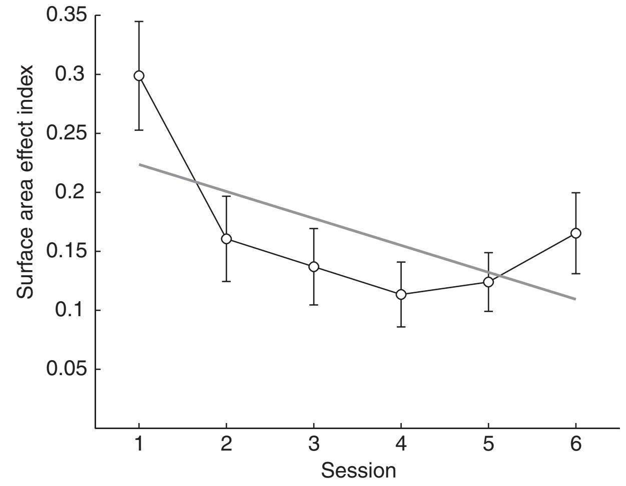

FIGURE 5 | Mean surface area effect index as a function of session number. The effect of surface area on accuracy decreased rapidly with the introduction of trial-by-trial feedback, plateaued after session 2, but remained low after feedback was removed on session 6. Gray line indicates the linear best fit accounting for repeated measures. Error bars indicate SEMs.

On a third of trials the cumulative surface area of the white dots and the black dots was equal. We looked at accuracy on this subset of trials in order to ascertain whether the improvement in *w* we observed was due solely to the decrease in bias caused by surface area, or whether other factors might also be contributing to improvement. We found that accuracy on area equal trials was well fit by a linear regression ($R^2 = 0.67$; $p \ll 0.0001$) and trended toward a significant positive slope ($b = 0.0043$; $p < 0.1$; without outliers $p < 0.05$). Closer examination of the data showed that the effect was not linear over sessions, but that all the improvement occurred between sessions 1 and 2. We ran a two-way ANOVA with factors for session and participant to confirm the effect of session on equal area accuracy [$F(5,95) = 4.81$; $p < 0.001$]. In *post hoc* *t*-tests we found that accuracy on area equal trials increased between sessions 1 and 6 (paired *t*-test, $p < 0.005$) and between sessions 1 and 2 (paired *t*-test, $p < 0.001$), but not between sessions 2 and 6 (paired *t*-test, $p = 0.80$). The rapid increase in accuracy between sessions 1 and 2 demonstrates a comparable time course to our findings for *w* and for the surface area effect index.

Overall, line length *w* scores (mean = 0.07, SD = 0.02) were much lower than number *w* scores (mean = 0.33, SD = 0.15) indicating that the line length task was easier. Despite having different absolute ranges, *w* for line length and numerosity were positively correlated on session 1 (**Figure 6A**), $r^2 = 0.44$, $p < 0.005$) and on session 6 ($r^2 = 0.38$, $p < 0.005$) consistent with a weak version of ATOM. Line length comparison tests were only given on the first and last session and subjects were never given trial-by-trial feedback on this task. Thus, any improvement from session 1 to session 6 on the line length task could be attributed to training on the number task and would thus reflect transfer across magnitudes as predicted by a strong version of ATOM. However, a comparison of *w* scores from the first session and the last session yielded no evidence of improvement in line length acuity (one-tailed paired *t*-test: $p = 0.283$). We examined the relationship between change in acuity on the numerosity task and change in acuity on the line length task in individual participants, but found no correlation (**Figure 6B**), $r^2 = 0.00$, $p = 0.99$) indicating that subjects who improved on the number task were no more or less likely to have improved on the line length task.

Accuracy on the line length task was very high on both the first and last sessions (mean correct = 93.6% and 93.9% respectively), which may have created a ceiling effect that obscured any improvement on the line length task from session 1 to session 6. We addressed this concern by assessing change in accuracy on only the most difficult 11:12 ratio line length comparison (mean accuracy 80.1%, SD = 10.6% and 84.6%, SD = 10.4% during sessions 1 and 6 respectively). Consistent with the original analysis, we found no evidence of improvement in accuracy on this subset of trials between sessions 1 and 6 (one-tailed paired *t*-test: $p = 0.12$). This confirms that number training caused no detectable improvement in line length acuity. Furthermore, there was no correlation between improvement in *w* scores for the number task and change in accuracy on these most difficult line length comparisons ($r^2 = 0.01$, $p = 0.68$).

Previous reports have demonstrated that standardized math scores correlate with numerical acuity in children (Halberda et al., 2008; Gilmore et al., 2010; Mazzocco et al., 2011b). One recent study also showed a positive correlation between *w* and mental arithmetic in adults however the relationship was mediated by ordinal symbol knowledge (Lyons and Beilock, 2011). Consistent with these reports we found a negative correlation between SAT/GRE score and *w* (**Figure 7A**, $r^2 = 0.28$, $p < 0.02$) and no correlation between verbal SAT/GRE score and *w* (**Figure 7B**,

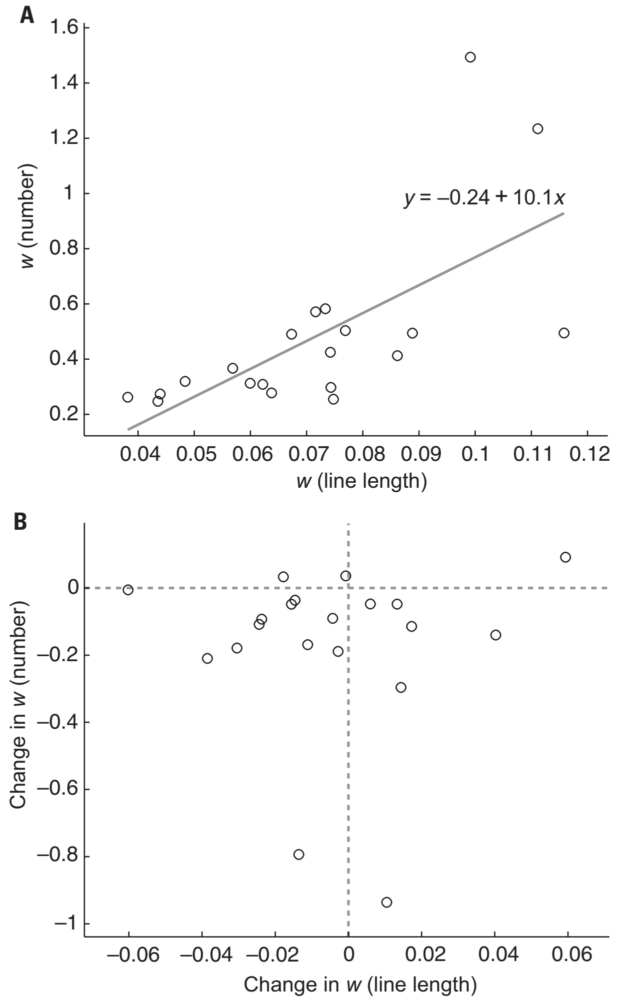

FIGURE 6 | (A) Numerosity w scores were positively correlated with line length w scores on session 1 ($r^2 = 0.44$, $p < 0.005$) and session 6 ($r^2 = 0.38$, $p < 0.005$, data not shown). Gray line is the best fit to the data and the equation shows the intercept and slope. **(B)** Change from session 1 to session 6 in numerosity w scores plotted against the change in line length w scores over the same period. Numerosity w scores were not correlated with any improvement in line length w scores ($r^2 = 0.00$, $p = 0.99$). Note that most participants (17/20) had a negative change in ANS w indicating an improvement. Change in line length w, however, was evenly distributed around 0 indicating no improvement in line length acuity in the population. Data points to the left of the vertical dotted line indicate an increase in line length comparison acuity whereas data points to the right indicate a decrease in line length comparison acuity from session 1 to session 6. Data points below the horizontal dotted line indicate an increase in numerosity comparison acuity whereas data points above indicate a decrease in numerosity comparison acuity from session 1 to session 6.

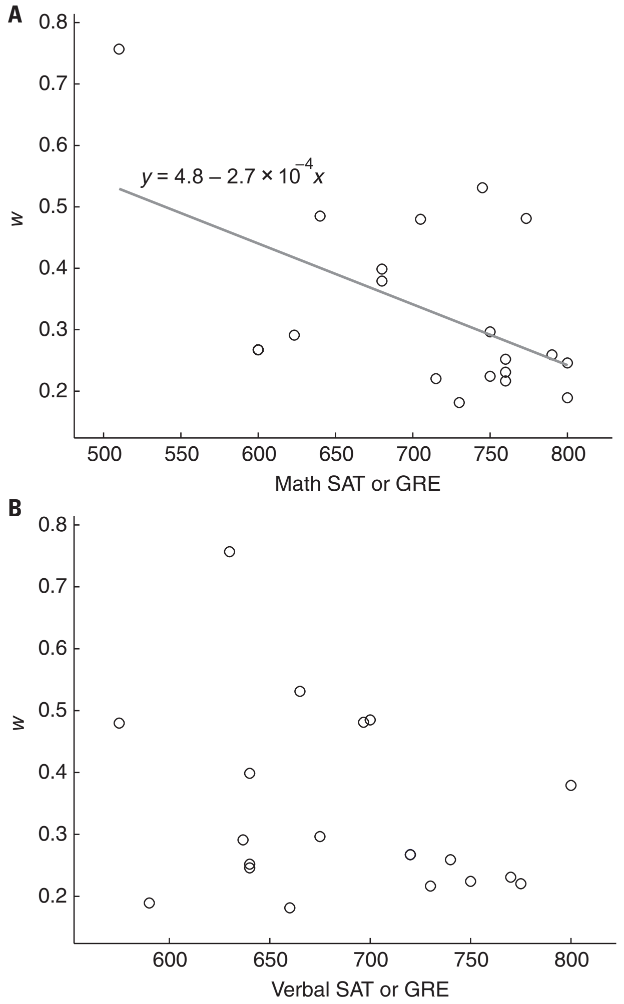

FIGURE 7 | (A) Standardized mathematics test scores (GRE or SAT) were negatively correlated with w ($r^2 = 0.28$, $p < 0.02$). Gray line is the best fit to the data and the equation shows the intercept and slope. **(B)** Verbal scores were not significantly correlated with w ($r^2 = 0.08$, $p = 0.23$).

$r^2 = 0.08$, $p = 0.23$). This negative correlation did not hold when the three participants with single-session outlier data were excluded (without outliers: $r^2 = 0.04$, $p = 0.47$). However, when w was recalculated for these three subjects excluding the single session for which each subject exhibited an outlier w score the negative correlation was significant with math SAT/GRE scores ($r^2 = 0.27$, $p < 0.05$), but not verbal scores ($r^2 = 0.08$, $p = 0.22$).

DISCUSSION

MALLEABILITY OF ANS ACUITY

The primary question our research addressed was the malleability of the Weber fraction in response to extended training. We found rapid improvement in ANS acuity with the introduction of trial-by-trial feedback and this improved performance was maintained in a final session when feedback was omitted. Very little improvement in ANS acuity occurred after the first session in which trial-by-trial feedback was introduced (second actual session) suggesting that ANS acuity may plateau and then be insensitive to extended training. Response time, however, continued to decrease with further training on the task. It remains possible that the four sessions of training with feedback that we provided was not sufficient and that additional training would have reduced the Weber fraction further even in these participants. It is also possible that extended training with feedback in children who have not yet reached asymptotic performance in ANS acuity would be more effective and we plan to pursue this in future research.

Why was the introduction of trial-by-trial feedback so powerful in reducing the Weber fraction? One caveat is that our study did not include a control group that did not get feedback. Therefore it is possible that initial practice, and not trial-by-trial feedback was the main factor in reducing *w* in the first session of the number task. Future studies should explore this possibility. Another possibility is that feedback allowed subjects to decrease reliance on total stimulus surface area. The effect of surface area and numerosity congruency was strong in the majority of subjects before trial-by-trial feedback was introduced. Thus subjects tended to view arrays with larger total surface area as more numerous. With training, however, the effect of surface area decreased, and by the final session participants no longer showed a surface area bias. The decrease in the congruence effect, however, cannot fully explain the observed decrease in *w*. On trials where the surface area of the two arrays was equal, we still observed an increase in accuracy after feedback was introduced, and, like the effect seen in *w*, this improvement in accuracy persisted after feedback was removed.

Decreasing reliance on total surface area as a mechanism for improving ANS acuity is consistent with theories of perceptual learning. Goldstone (1998) identified attentional weighting and differentiation as potential mechanisms for perceptual learning. Changes in attentional weighting can allow participants to focus on crucial information like numerosity while ignoring irrelevant stimulus features like surface area. Differentiation allows previously indistinguishable aspects of stimuli to be perceived as distinct and has been shown to apply to different perceptual dimensions of the same stimulus. For example, according to the Munsell color system colors vary along three orthogonal dimensions: chroma, value, and hue. Burns and Shepp (1988) found that trained subjects were significantly better at differentiating value and chroma than untrained subjects. Similarly, subjects trained to categorize color based on chroma but not value increased their acuity in discriminating different chroma (Goldstone, 1994). These results suggest that our participants may be learning to differentiate the related dimensions of numerosity and surface area allowing them to ignore the extraneous surface area cues and to selectively improve number acuity.

Prior studies have examined the relationship between surface area and perceived numerosity in adults and come to different conclusions. Consistent with our findings, Hurewitz et al. (2006), found that congruence between surface area and number improved accuracy whereas incongruence caused a decrement in performance. Tokita and Ishiguchi (2010), however, found the opposite effect, that larger items were perceived as less numerous. Barth (2008) failed to find any effect of surface area congruence in an ordinal numerosity task. As Tokita and Ishiguchi (2010) demonstrated and we confirm here, trial-by-trial feedback rapidly diminishes or abolishes surface area bias. It remains an open question, however, exactly what stimulus or presentation factors determine the direction or existence of surface area bias effects in naïve subjects. One potentially important difference between our study and the Tokita and Ishiguchi (2010) study was that we presented dot arrays simultaneously and spatially overlapped whereas Tokita used sequential presentation.

It is interesting to note that studies with children suggest that the ability to separate dimensions improves with age (Smith and Evans, 1989; see Goldstone, 1998 for review). Thus children may be more susceptible to the surface area numerosity congruence effect than adults, and this effect may diminish with development and increasing acuity of the ANS. A large literature addresses the effect of surface area on number judgments across development. However, there is no consensus on how these interactions change with experience (e.g., Piaget, 1965; Mix et al., 2002; Cantlon et al., 2010).

THE ANS AND OTHER MAGNITUDE SYSTEMS

A second question our study addressed was the relationship between ANS acuity and the precision of line length comparisons. We found that performance on a line length task was positively correlated with performance on the ANS task. The introduction of feedback on the numerosity task, however, improved acuity for the numerosity task but did not generalize to the line length discrimination.

Walsh's (Walsh, 2003; Bueti and Walsh, 2009) theory of magnitude (ATOM) asserts that dimensions such as time, number, and space are processed by a common analog magnitude system and depend on a common set of parietal brain systems. The association between the spatial and numerical dimensions has been particularly well established (for review, see Hubbard et al., 2005). Many studies have demonstrated interference between numerical and spatial information, the SNARC effect being the most well-known (Dehaene et al., 1993). Parietal lesions causing hemi-spatial neglect often cause congruent neglect in the mental number line, implicating common parietal circuits in both spatial and numerical cognition (Zorzi et al., 2002; Cappelletti et al., 2007). Disruption of normal parietal function with rTMS causes deficits in comparing line lengths and numerosities (Dormal et al., 2011). Brain imaging studies have also implicated overlapping areas of the parietal cortex in both length and numerical comparison tasks (Fias et al., 2003; Dormal and Pesenti, 2009).

Our finding that line length acuity correlated with ANS is consistent with the theory that spatial and numerical comparisons depend on shared cognitive mechanisms. However, the improvement that emerged from the introduction of trial-by-trial feedback did not transfer to the line length task. This finding is consistent with a weaker version of ATOM in which magnitude comparisons share some common basis but at least in adulthood are differentiated. One possible explanation of this partial differentiation is that a single common comparator system is utilized in all judgments of relative magnitude regardless of dimension, but that each magnitude is represented by a dimension specific subsystem. Thus, although number and line length are represented along distinct mental continua, comparisons of two numbers or line lengths are mediated by a single common comparator. Under this framework, the correlation between ANS acuity and line length acuity is explained by the resolution of a common comparator. In contrast, trial-by-trial feedback in the numerosity comparison task results in improvements that are specific to numerosity representations (e.g., increasing precision of the underlying representations or narrowing in of attention to the numerosity dimension as opposed to surface area). Future work might be able to disentangle the effects specific to a mental magnitude comparison and the precision of representations of a specific mental magnitude by, for example, comparing the accuracy of a numerosity estimation task (how many dots?) and a numerosity comparison task, like the one we used. If the underlying representation of number narrows due to training, then it should to transfer across different number tasks.

An important caveat is that our control task had some significant limitations. One limitation was that we were only able to test one non-numerical magnitude judgment (i.e., line length), and we did not assess a non-magnitude perceptual judgment. This prevented us from determining whether the correlation between the number and line length Weber fractions was due to global cognitive influences such as attention or fatigue, or alternatively arose from common magnitude processing mechanisms. Furthermore, we equated the ratios for the numerical and line length stimuli and this meant that the line length stimuli were significantly easier to discriminate than the numerical stimuli. One reason for this apparent disparity in difficulty may be that to solve the numerical task participants had to ignore total surface area which was carefully controlled, whereas in the line length task there was no competing dimension. However, when we analyzed the most difficult line length trials we found to improvement in accuracy indicating that the lack of transfer was not due to a ceiling effect in the line length task. Future studies should include additional control tasks and match difficulty and stimulus complexity to make firmer conclusions about the import of the positive correlation we observed between ANS and line length judgments.

RELATIONSHIP BETWEEN THE ANS AND SYMBOLIC MATH

A third question our findings address is the relationship between ANS acuity and symbolic mathematics. Recent work has demonstrated that ANS acuity is positively correlated with a variety of mathematical abilities in children and adults (Halberda et al., 2008; Gilmore et al., 2010; Lyons and Beilock, 2011; Mazzocco et al., 2011a,b). These studies suggest the ANS may serve as a developmental building block upon which symbols are mapped and that precision in ANS representations facilitates symbolic mathematics (e.g., Dehaene, 1997; Wynn, 1998; Gilmore et al., 2007; Verguts and Fias, 2008; Mundy and Gilmore, 2009). A great deal of work is still needed to probe the dynamics of this relationship and to specify the mechanisms by which ANS acuity might scaffold symbolic mathematics. Consistent with these prior recent studies, our sample of adult participants exhibited a positive correlation between ANS acuity and standardized math scores but not verbal scores. Future work should explore the functional relationship between the ANS and mathematics by assessing whether improving ANS acuity, perhaps earlier in development, bestows any benefits for symbolic mathematics (e.g., Wilson et al., 2006a,b; Kucian et al., 2011).

There are several possible explanations for why we did not find a more robust relationship between standardized mathematics scores and w. We had to combine SAT scores with GRE scores, since a few of our participants had not taken the SAT. Although the tests are similar and graded on the same scale (200–800 points), combining GREs and SATs certainly added noise to the measure. In addition, our sample did not contain much variance in math scores, and may have suffered from a ceiling effect. Only one participant had a math score below 600, whereas fully half our sample scored 750 or above. Thus future studies should recruit larger samples from a more heterogeneous population.

ABSOLUTE VALUE AND RELIABILITY OF *w*

Global w scores for our sample fell between 0.18 and 0.76 with a mean of 0.33 and a standard deviation of 0.15. This is higher than most previous estimates for young adults, which cluster below 0.2 (for review and meta-analysis, see Piazza and Izard, 2009) but was similar to the range of 0.22–1.5 measured by Gilmore et al. (2011) in their non-symbolic comparison task. The disparate ranges in these three studies are surprising given the similarity of the estimation tasks.

One possible reason we observed higher w is that we did not control the dot density of our stimuli. Our two stimuli were generated within a single circle 300 pixels in radius. As a result the total extent of each stimulus was equal, but the density of the stimulus was negatively correlated with numerosity. Previous research has demonstrated that loosely spaced dots appear greater in number than densely packed dots (Krueger, 1972; Ginsburg, 1976). If the density of each set of dots was viewed independently (e.g., adding black dots did not increase the perceived density of the white dots) then this effect may have inflated estimates of our less numerous stimuli, which would have appeared less densely packed and therefore more numerous thus impairing discriminability. Lower accuracy would have increased our estimate of w. This effect may have been especially pronounced in our stimuli because they had a relatively large degree of visual crowding. Further research into the specific effects relative density and other low level stimulus features on ANS acuity may help clarify differences in average w in different experiments.

We also measured the reliability of w scores by comparing split-halves of individual session data. Single session reliability estimates were high and similar to estimates obtained in previous reports (Maloney et al., 2010; Gilmore et al., 2011). Note that one other report obtained low estimates of split-half reliability, however they used the distance effect rather than w as a measure of ANS acuity (Sasanguie et al., 2011). Our repeated testing design allowed us to assess reliability in w across six sessions over a 2-week period. Despite the reduction in w from session 1 to session 6 there was strong positive correlation in these scores demonstrating test–retest reliability over a 2-week period. These data thus provide evidence of both stable and malleable components of ANS acuity.

POTENTIAL SINGLE NEURON CORRELATES

Single cells in the monkey brain appear to encode quantity. The firing rate of cells in or near the intraparietal sulcus in macaque monkeys are systematically correlated with the numerosity of dot arrays (Nieder and Miller, 2004; Roitman et al., 2007), the numerosity of sequential actions (Tanji et al., 2002) or sequentially presented stimuli (Nieder et al., 2006), and line length (Tudusciuc and Nieder, 2007). Prefrontal cortical cells also encode numerosity (Nieder et al., 2002) and more abstract magnitudes such as symbol numerosity mappings (Diester and Nieder, 2007), and ordinal rules (Bongard and Nieder, 2010).

There are several different ways in which we can imagine single cell number coding systems to yield improved performance as a result of training. Neurons found in the IPS and PFC are tuned to individual numerosities. Tuned number neurons fire maximally for a particular numerosity and decrease firing in response more distant numerosities. One possibility is that the behavioral improvements we observed as a result of trial-by-trial feedback are achieved by sharpening the tuning curves of these neurons. As a result they would fire less for neighboring numerosities and be more selective for their preferred numerosity after training. Alternatively, training and feedback may recruit more individual neurons to the representation of number. This could improve the precision of the population code without affecting the width of the tuning curves of individual number selective neurons.

Other neurons in lateral intraparietal area (LIP) have been shown to encode numerosity monotonically, with separate populations either increasing or decreasing firing rate with the observed numerosity (Roitman et al., 2007). Monotonic numerosity neurons have been hypothesized to play the role of numerosity accumulators in several models of numerical cognition (Meck and Church, 1983; Dehaene and Changeux, 1993; Verguts and Fias, 2004). The accumulation layer in these models plays an intermediary role between perception of the stimulus and the final tuned representations of individual numerosities. Improved performance as a result of training might emerge from a sharpening of these accumulator-like neurons in LIP. After training, a given difference in numerosity would generate a greater increase (or decrease) in the firing rate in LIP neurons. An increase in the steepness of these monotonic functions could increase discriminability between numerosities and in turn lead to sharper tuning functions in downstream areas, including other areas in the IPS and in prefrontal cortex. Pearson et al. (2010) demonstrated that LIP like monotonic functions are in principle sufficient for completing a numerosity bisection task. This raises the possibility that different numerosity representations may be generated idiosyncratically in response to particular task demands, and training and education may play an important role in determining which types of number representations become realized in the brain.

Tudusciuc and Nieder (2007) found both line length and numerosity neurons in macaque intraparietal cortex. However, they did not find neurons representing magnitude abstractly along a common mental magnitude line. Line length and numerosity were represented in separate neuronal populations. A small percentage of neurons represented both line length and numerosity, but these neurons were tuned to different line length and numerosity magnitudes: a neuron that coded for a short line length was equally likely to code for a small or a large numerosity. Thus, in monkeys it seems that line length and numerosity magnitudes do not share a common encoding scheme on the single neuron level in IPS. If one of the mechanisms of acuity improvement outlined above selectively acted on the numerosity neurons in the IPS but not the line length neurons, this could explain the failure of acuity improvement to transfer from one magnitude dimension to another.

CONCLUSION

Our study addressed the malleability of the ANS and the relationship between the ANS and other judgments. We found that ANS acuity showed rapid improvement with the introduction of trial-by-trial feedback but that it was otherwise relatively impervious to extended training in adults. The improvement in w in response to feedback was at least partially due to a decrease in reliance on surface area as a cue for numerosity, although other factors also influenced improvement. Acuity in a line length discrimination was positively correlated with ANS acuity, however, improvement in the ANS in response to feedback did not transfer to improvement in this spatial magnitude discrimination, providing further evidence that magnitude judgments may have both shared and distinct components. Finally, even in our relatively small sample of 20 subjects, acuity of the ANS was positively correlated with standardized tests of mathematical but not verbal proficiency. These findings raise important questions about the malleability of the ANS over the lifespan and the relationship between the ANS and uniquely human mathematical abilities.

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Micro and macro pattern analyses of fMRI data support both early and late interaction of numerical and spatial information

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Numbers and space are two semantic primitives that interact with each other. Both recruit brain regions along the dorsal pathway, notably parietal cortex. This makes parietal cortex a candidate for the origin of numerical–spatial interaction. The underlying cognitive architecture of the interaction is still under scrutiny. Two classes of explanations can be distinguished. The early interaction approach assumes that numerical and spatial information are integrated into a single representation at a semantic level. A second approach postulates independent semantic representations. Only at the stage of response selection and preparation these two streams interact. In this study we used a numerical landmark task to identify the locus of the interaction between numbers and space. While lying in an MR scanner participants decided on the smaller of two numerical intervals in a visually presented number triplet. The spatial position of the middle number was varied; hence spatial intervals were congruent or incongruent with the numerical intervals. Responses in incongruent trials were slower and less accurate than in congruent trials. By combining across-vertex correlations (micro pattern) with a cluster analysis (macro pattern) we identified large-scale networks that were devoted to number processing, eye movements, and sensory–motor functions. Using support vector classification in different regions of interest along the intraparietal sulcus, the frontal eye fields, and supplementary motor area we were able to distinguish between congruent and incongruent trials in each of the networks. We suggest that the identified networks participate in the integration of numerical and spatial information and that the exclusive assumption of either an early or a late interaction between numerical and spatial information does not do justice to the complex interaction between both dimensions.

Keywords: cluster analysis, early interaction, interaction between number and space, late interaction, multi-voxel pattern analysis, numerical landmark task

INTRODUCTION

Large parts of the human brain are dedicated to the analysis of visual information and the guidance of motor behavior. The extraction of spatial and metric characteristics of the objects in a visual scene is crucial for successful motor actions. Depth cues and retinal size information, for example, are integrated to inform about the actual physical size as well as the position of a given target object, and allow us to successfully grasp it. Beyond the spatial information of a visual scene, recent studies suggest that number is another primary feature of vision (Burr and Ross, 2008; Ross and Burr, 2010). A number of studies suggest that numerical and spatial representations are not independent of each other but do interact in various ways (Hubbard et al., 2005). Few neuroimaging studies directly investigated this consensual notion, focusing mostly on the overlap between physical and numerical size (Pinel et al., 2004; Hubbard et al., 2005; Kaufmann et al., 2005, 2006, 2008; Cohen Kadosh et al., 2007). The current study aimed at investigating the interaction between numbers and space and tried to identify the locus of the interaction between both domains. Locus here refers to both the stage in the stream of information processing (sensory, central, response) as well as the brain region where both dimensions exhibit representational overlap.

The Spatial–Numerical Association of Response Codes (SNARC) effect is often taken as an indicator for an association of numerical magnitude with external space (Dehaene et al., 1993): left side responses are faster for small numbers while right side responses are faster for larger numbers. This has been interpreted by many authors as evidence for a left-to-right oriented “mental number line” with smaller numbers placed to the left of larger numbers (at least in left-to-right reading cultures; Shaki and Fischer, 2008; Shaki et al., 2009). While some authors argued that the observed link between numbers and space relies on the congruence of the response codes with an intermediate categorical polarity representation (Proctor and Cho, 2006; Santens and Gevers, 2008), it has been demonstrated that this link prevails in paradigms where response and stimulus representation are orthogonal to each other (Nicholls et al., 2008) and in paradigms that did not use spatially encoded manual responses (Stoianov et al., 2008). The concept of the mental number line also proved useful in explaining the impact of numerical information on spatial attention. When asked to indicate the appearance of a stimulus that appeared to the left or right of a centrally presented number, participants responded faster to right-sided stimuli that followed a large number as compared to right-sided stimuli that followed small numbers (Fischer et al., 2003). An equivalent advantage for left-sided stimuli following small numbers was observed. Fischer et al. (2003) attributed this finding to the automatic activation of a number's position on the spatially oriented mental number line which in turn caused a shift of the focus of attention on the mental representation accompanied by a shift of attention in the visual field. Together this points to a mental representation of numbers that entails spatial characteristics and affects perception and behavior. Song and Nakayama (2008) measured the trajectories of pointing movements to a lateralized target in response to a numerical comparison task (smaller or larger than five) with a centrally presented number. They observed that with decreasing numerical distance the initial trajectory approached the central location and was corrected in direction of the target during later periods of the movement. It seems that the spatial position of the number on a mental representation (i.e., the mental number line) has a significant and dynamic impact on the movement trajectory. This demonstrates the automatic (i.e., non-voluntary) influence of mental representations on information processing up to the execution of motor responses. The idea that numerical and spatial representations overlap and interact is supported by the finding that numerical magnitude primes various aspects of motor responses such as grip aperture (Andres et al., 2004; Lindemann et al., 2007) and grip force (Vierck and Kiesel, 2010). In general, these results imply that both physical size of an object and numerical magnitude are automatically processed and influence each other.

The presence of two basic cognitive effects, i.e., the distance and the size effect in both dimensions (number and space) supports the idea of overlapping representations. The distance effect describes the fact that – either in spatial or in numerical terms – the closer two objects are in size the more difficult it is to indicate the larger one. The size effect describes the phenomenon that a constant level of accuracy in size comparison tasks is achieved only when the distance between both objects increases proportionally with increasing absolute size. The universality of these effects, which can also be found in the temporal domain, has lead to the assumption of common cortical metrics for space, numbers, and time (Walsh, 2003).

At the neuro-functional level, spatial overlap between systems that are activated when either numerical or spatial information is processed has been interpreted as evidence for overlapping mental representations. Using positron emission tomography, Fias et al. (2003) observed overlapping activity along the intraparietal sulcus (IPS) for symbolic and non-symbolic numbers as well as for line lengths and angles. In a similar vein, Cohen Kadosh et al. (2007) reported functional brain activations using functional magnetic resonance imaging (fMRI) in posterior parietal cortex when participants compared two digits in terms of numerical size, physical size, or luminance. One might argue, however, that the mere co-activation of a given region by different dimensions does not necessarily imply the recourse of both dimensions on identical neural circuits. The coarse spatial resolution of fMRI does not allow for identification of overlapping but separate neural circuits in a single voxel. That is, any observed co-activation can equally well be explained by either identical neural circuits that are activated by several contrasts or by independent circuits that occur in the same voxel. More fine-grained multivariate analysis approaches might prove useful in this context.

The size-congruity effect (SCE) has often been used to explore the interaction between numbers and space. When asked to decide on the physically larger of two visually presented numbers, participants' responses are significantly slower for incongruent stimulus pairs such as 2 and 9 as compared to congruent stimulus pairs like 2 and 9. While nine is the numerically larger number in both cases, the comparison of the physical sizes points to the two in the first and to the nine in the second pair, giving rise to a response conflict for the former stimulus pair (Foltz et al., 1984). In this type of paradigm one distinguishes between two stimulus dimensions (e.g., numerical and physical size) which interact with each other. An interesting question concerns the locus of this interaction. Broadly speaking, two scenarios have been proposed. The early interaction approach assumes that numerical and physical size are integrated into a single representation at a semantic level (Schwarz and Heinze, 1998). The late interaction approach assumes that the two dimensions are processed in parallel and an interaction (or integration) occurs only at the response level (e.g., Ridderinkhof, 2002).

Evidence for a joint neural circuit processing both numerical and other extensive dimensions comes from fMRI studies that show that the SCE itself modulates activity in the IPS (Pinel et al., 2004; Kaufmann et al., 2005). Again, the authors mainly report overlapping activity in support of this notion. In an event-related potential study (ERP), Schwarz and Heinze (1998) found that congruity between numerical and spatial size of the presented digits affected the latency of the P300 component over centro-parietal electrodes. Since the amplitude of the P300 component is thought to vary with numerical distance in the context of numerical cognition experiments (Grune et al., 1993), this result supports the idea of an early interaction between numerical and size information. Conversely, Schwarz and Heinze (1998) did not observe any response preparation due to the irrelevant dimension in the lateralized readiness potentials, again speaking against the late interaction hypothesis. It should be noted that the absence of response preparation for a response activated by the irrelevant dimension in the ERPs does not necessarily mean that earlier response stages remained unaffected by the congruence between numerical and physical size. The particular orientation of a putative dipole in supplementary motor areas (SMAs), for example, might prevent any observable amplitude difference on the scalp.

On the other hand, a number of studies support the idea of late interaction of two conflicting sources of information from a single stimulus. By adopting thorough analyzes of the distribution of reaction times and error rates, Ridderinkhof (2002) reported results that strongly implied a late interaction between relevant (e.g., stimulus color) and irrelevant (e.g., stimulus location) stimulus parameters. In particular, this approach postulates that the conflicting information is integrated and the conflict resolved only at a very late, response-related stage of information processing. Additionally, Ridderinkhof (2002) proposed an active suppression mechanism that selectively operates on the irrelevant stimulus dimension and helps to suppress conflicting (i.e., erroneous) response tendencies, a view that is supported by results from Notebaert and Soetens (2006). They observed a reduced impact of the irrelevant stimulus dimension in trials that followed the response in incongruent trials with a very short temporal interval only (50 ms). This is thought to reflect the consequences of the lingering inhibition of the irrelevant dimension. Recently, Forstmann et al. (2008) used MRI to demonstrate that structural and functional brain parameters characterizing the right inferior frontal cortex were systematically related to the individual model parameters that quantified the inhibition of irrelevant information in a Simon task. In a combined fMRI and ERP study using a size-congruity paradigm, Cohen Kadosh et al. (2007) found an interaction of numerical and physical size in parietal regions as well as in motor regions, implying late interaction at the response stage. This effect was modulated by cognitive load, however, with the late interaction hypothesis being supported only with low cognitive load. Knops et al. (submitted) employed a paradigm in which participants had to decide on the larger of two intervals in a number triplet. The triplet was presented visually and the horizontal position of the middle number was varied. Hence the physical intervals between the middle number and the outer numbers could be congruent or incongruent with the corresponding numerical intervals (see **Figure 1**). When asked for the numerical intervals, incongruent trials were responded to slower and more error prone, implying that the irrelevant physical information had an impact on the numerical decision. No such influence was observed when participants had to decide on the physical intervals. Participants were significantly faster in deciding on the physical intervals than in deciding on the numerical intervals, which might explain the observed asymmetry. In sum, the results from this experiment suggest a dual route mechanism with late interaction between numerical and spatial information.

Beyond the opposing views of an early or late interaction between different (and sometimes conflicting) stimulus dimensions, a recent review article (Cohen Kadosh et al., 2008) concluded that both shared and distinct magnitude mechanisms may co-exist. On a neurobiological level this view received support from recent single-unit recordings in monkeys. Tudusciuc and Nieder (2007, 2009) reported neurons in parietal and frontal cortex that coded for numerosity, for line length or for both types of information at the same time.

In the current fMRI study we want to shed light on the functional architecture subserving the interaction between numbers and space. To this end we propose a new multivariate analysis approach that might prove useful in the identification and analysis of functional networks. We used a so-called numerical landmark task, revealing robust behavioral interactions between the processing of numerical and spatial distances (Lonnemann et al., 2008). No study so far has shown the neural correlates of the putative association between numerical distances and spatial distances. Since parietal cortex seems to play a central role in the processing of numbers and space, we employed a scanning protocol with a relatively small voxel size (2 mm × 2 mm × 2 mm) that allows for a more fine-grained functional parcellation of different areas in parietal cortex as compared to previous studies. In combination with cortex-based alignment and the analysis of unsmoothed data, such a protocol offers the opportunity to delineate in more detail sub-divisions of parietal cortex and their particular role in the context of numerical–spatial interactions. The chosen voxel size also allowed for the adoption of multivariate analysis approaches, offering a more comprehensive data analysis than the standard voxel-wise univariate general linear model (GLM) approach. Previous fMRI studies mainly reported overlapping activations from GLM analyses in parietal cortex and interpreted this as evidence for shared representations. Overlapping activations, however, can have multiple origins and do not necessarily imply shared neural circuits. A multivariate analysis of the spatial pattern of activations appears to be better suited to detect shared functional circuits. Temporal resolution of fMRI is poor and by itself does not allow for an analysis of the temporal dynamics of the brain. By combining across-voxel correlations and cluster analysis we may be able to identify large-scale functional networks in the brain that can be associated with either stimulus integration or response-related processes. That is, by thoroughly analyzing brain activation in response-related and stimulus-related structures we aimed at investigating the locus of the numerical–spatial interaction.

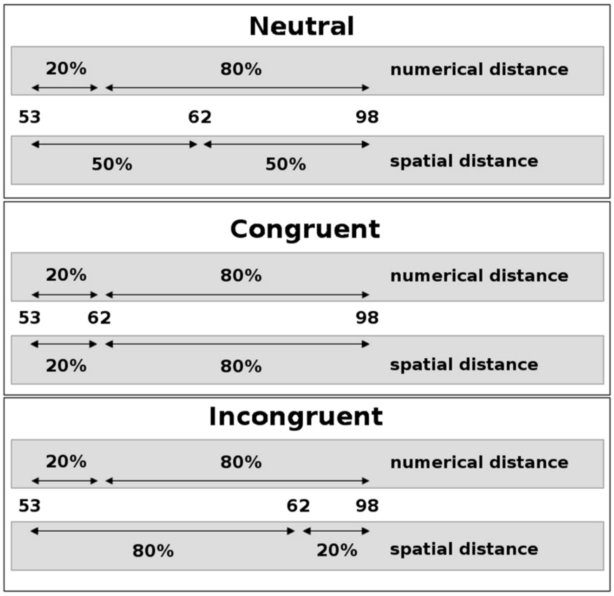

FIGURE 1 | Schematic depiction of the numerical landmark paradigm. The spatial position of the middle number of a number triplet (here: 62) was varied such that the spatial intervals to the outer numbers (here: 53 and 98) could be neutral (top), congruent (middle), or incongruent (bottom) with the respective numerical intervals. Percentages relate the respective intervals to the size of the interval between the outer numbers. Participants were asked to decide which side the smaller numerical interval is on.

MATERIALS AND METHODS

PARTICIPANTS

After having given their written informed consent eighteen (nine female) right-handed participants [mean age 26.1 (19–32) years] participated in this study, which was approved by the local Ethics Committee of the Medical Faculty, RWTH Aachen University. Three participants (one female, two male) were excluded from all subsequent analyses due to head movement artifacts. All participants had normal or corrected to normal vision and no neurological or psychiatric history.

EXPERIMENTAL DESIGN

Cerebral activations were studied for three different tasks, two localizer tasks (subtraction, saccades), and a numerical landmark test. Participants were introduced to all of the tasks before fMRI scanning. The numerical landmark test was conducted in an event-related design and divided in two identical blocks of 120 trials each. The two localizer tasks were administered in a block design. Each of the localizer tasks was compared to a control task matched for stimulus characteristics. During an fMRI scanning sequence, eight blocks (12 trials each) were presented with an alternation of primary task and control task blocks (four blocks each). Breaks of 20 s separated the different blocks. Each participant started with the numerical landmark test, while the sequence of the remaining tasks was counterbalanced across participants. Stimuli were presented via a head-mounted video display designed to meet MR requirements. The whole experimental procedure lasted approximately 90 min and was controlled by Presentation® software (Neurobehavioral Systems, Inc.).

Numerical landmark task

In the numerical landmark task participants had to decide which one of the two numerical distances in a number triplet was numerically smaller. The stimulus set consisted of 16 two-digit number triplets spatially arranged in a horizontal fashion on the screen at two varying spatial intervals between the middle number and the outer two numerals (see **Figure 1**). The constituting numerals of a triplet were always arranged in numerically ascending order from left-to-right. Numerical and spatial distances were manipulated independently. As a result, numerical and spatial intervals could be congruent or incongruent. In neutral triplets, spatial intervals were identical. The stimulus set was identical to the one used in a previous study (Lonnemann et al., 2008) but presented twice. The participants had to indicate the side where the numerical distance was smaller by pressing a response button with the left index finger when it was smaller on the left side and by using the right index finger when it was smaller on the right side. Instruction stressed both speed and accuracy. Digits were presented in white color against an otherwise black background and had a visual angle of 0.7° in height and of 0.5° in width. The two blocks of 120 trials each were separated by a break of 1 min. Each block included 24 null-events, in which a black screen was presented. A trial started with the presentation of a fixation cross for 500 ms. After the fixation cross had vanished, the target appeared until the response, but only for a maximum duration of 3000 ms, followed by a black screen for a varying time interval [500, 1000, 1500, 2500, 3500, or 6000 ms (mean = 2500 ms)].

Subtraction task

In the subtraction task, stimuli were white Arabic digits from 2 to 9 with a visual angle of 0.7° in height and of 0.5° in width presented at fixation and against a black background. Each trial started with the presentation of a digit appearing for 150 ms, which was then replaced by a fixation cross. Participants were instructed to subtract the respective number from 11 and to name the result mentally within 3000 ms. In the control naming task, stimuli were uppercase letters between B and J, excluding I. Participants were asked to name each letter mentally.

Saccades task

In the saccades task participants were shown eight boxes (each with a visual angle of 1.2° in width and height) arranged in a circle at 6° eccentricity from a similar box positioned at the center of the screen. Each trial started with the presentation of a white square appearing within a randomly chosen box for 150 ms, which was replaced by a fixation cross centered in the box. The participants were asked to move their eyes toward this box and fixate it for 2000 ms until the next trial appeared. In the control fixation task, participants had to fixate the center position while white squares appeared in the peripheral positions following the same order as in the primary task.

IMAGING PROTOCOL

Functional images were acquired on a 3-T Philips Gyroscan NT with a SENSE head coil. Transversal multi-slice T2*-weighted images were obtained with a gradient echo planar imaging sequence (TE = 30 ms; TR = 2 s; 80 × 80 matrix; flip angle = 90°; 24 slices, 2 mm × 2 mm in-plane resolution; slice thickness 2 mm) covering most of the frontal, of the parietal, and of the occipital lobe. During the numerical landmark task 780 volumes were acquired, while in each of the other two tasks 250 volumes were recorded. Each part of a session started with five dummy scans to allow tissue to reach steady state magnetization. These scans were not recorded for data analysis. A high-resolution T1-weighted three-dimensional anatomical image was also acquired (TE = 4.59 ms; 256 × 256 matrix; voxel dimensions = 1 mm × 1 mm × 1 mm).

DATA ANALYSIS

Behavioral data

Analyses of variance (ANOVAs) and *post hoc* tests for further investigations were conducted separately for reaction time (henceforth RT) and error rate (henceforth ER). ER was arcsine-transformed ($2\arcsin\sqrt{\text{error rate}}$). The Huynh–Feldt epsilon (ε) was computed to correct the degrees of freedom of the F-statistics in case of significant violation of the sphericity assumption. To minimize the risk of alpha error inflation due to multiple *post hoc* testing we applied the sequentially rejective Bonferroni method by Holm (1979) to all reported *post hoc* tests. We report only significant results. Only correct responses were used for calculating mean RT. Trials in which no response occurred were classified as errors. Responses below 200 ms were excluded from further analysis, as well as responses outside an interval of ±3 SDs around the individual mean. A total of 0.7% of the response was excluded.

Neuro-functional data

BrainVoyager QX 1.9 software (Brain Innovation, Maastricht, The Netherlands) was used to analyze neuroimaging data (Goebel et al., 2006). Preprocessing was done separately for each of the three parts of a session and included slice scan time correction (using cubic spline interpolation), temporal high-pass filtering, and three-dimensional-motion correction. Estimated translation and rotation parameters never exceeded 2 mm. Functional datasets were co-registered to the Talairach-transformed anatomical image. All individual brains were segmented at the gray/white matter boundary using a semiautomatic procedure based on intensity values (ITK-SNAP; Yushkevich et al., 2006). The cortical surfaces were reconstructed, inflated, and flattened with BrainVoyager QX 1.9 software. A high-resolution cortical alignment (CBA) method using curvature information reflecting the gyral/sulcal folding pattern was used to improve correspondence across brains beyond Talairach space matching. Using unsmoothed data, this kind of cortex-based analysis has been shown to reveal spatially more confined group clusters of activation (Goebel et al., 2006). Using CBA offers has major advantages over standard Talairach normalization. First, by respecting the anatomical folding pattern of the individual brain anatomy the spatial relations of any given pair of vertices on the resulting two-dimensional structure reflect their spatial relations as observed in the cortex. For example, two points on opposite walls of a given sulcus may unwarrantedly be interpreted as being spatially close to each other when using standard Talairach normalization since the gyral/sulcal folding pattern is not taken into account. Using CBA, however, the two points will not appear next to each other but the true distance between them – that roughly corresponds to twice the depth of the sulcus – will be respected. Second, Talairach normalization results in poor anatomical precision (Fischl et al., 1999). The large mismatch of spatial correspondence between important anatomical landmarks after Talairach transformation is usually compensated by applying spatial smoothing of functional data. However, spatial smoothing affects the spatial resolution of data which is of disadvantage when smaller voxels are used as is the case in the present study. The use of spatially unsmoothed data with high spatial resolution is recommended when classifiers are used. CBA can create a high amount of anatomical correspondence between individuals without spatial smoothing and is therefore ideally suited for the use of decoding methods such as multi-voxel pattern analysis (MVPA, see below). It should be noted that we used vertices rather than voxels as features for classification. Hence, MVPA will be used throughout the article as acronym for multi *vertex* pattern analysis but it refers to the same family of decoding techniques (e.g., support vector classification) as multi-*voxel* pattern analysis.

Activation data were submitted to a classical GLM approach and projected on the mean cortex-based aligned brain anatomy of the 15 participants. To visualize the functional network activated by the numerical landmark task we report the results of the conjunction between the contrasts congruent > baseline and incongruent > baseline. The calculation network was visualized by the contrast calculation > control. The saccades network was visualized by the contrast saccades > control. We applied a surface-based version of the cluster size exclusion method used for multiple comparisons correction as introduced by Hagler et al. (2006) to all random effects contrasts with voxel-wise $p = 0.005$. This method estimates the cluster size limit at a desired statistical threshold and validates it by means of Monte Carlo simulation (500 iterations).

The GLM approach is a powerful tool to analyze the differences between two conditions in terms of activation *amplitude*. It lacks, however, the capacity to integrate the numerous relations between vertices in a given region of interest (ROI) that form specific spatial or temporal *patterns of activations* which in turn characterize a cognitive task. Recent approaches to the analysis of multivariate brain imaging data emphasize that different tasks, conditions, and even stimuli give rise to distinct and recognizable patterns of activations even in situations when the GLM approach is not sensitive enough to reveal amplitude differences (Peelen et al., 2006; O'Toole et al., 2007). Especially with cognitively close conditions it is not plausible to assume large differences in the distribution of distinct networks of neurons which would cause differences in amplitude between two regions or huge differences in the BOLD responses to specific conditions. It is very likely that closely intermingled cortical circuits elicit very similar activations for two conditions when looking only at the amplitude of the BOLD response. By taking into account the specific spatial pattern of activity across a larger set of vertices in a ROI one might therefore increase the sensitivity to detect fine-grained differences between two conditions. We defined six ROIs in both hemispheres. The parietal cortex along the IPS was subdivided into four distinct, non-overlapping ROIs (see **Figure 2B**). Two ROIs cover horizontal aspects of parietal cortex [horizontal aspect of the IPS (HIPS), aHIPS], that is thought to play a major role in the representation of numerical magnitude (Hubbard et al., 2005). Two ROIs were chosen that are frequently linked to response selection, response preparation, and motor planning, i.e., SMA and the anterior aspect of the IPS, area AIP/BA 2. Finally, two ROIs were defined that cover (1) the parietal saccades system that appears to be play a role also in the attribution of spatial attention along the mental magnitude representation, the posterior superior parietal lobule (PSPL) of the IPS, as well as (2) the frontal saccades system, i.e., the frontal eye fields (FEF). In detail, the vertices for the different ROIs were chosen as follows. Active vertices from the calculation localizer in the HIPS were attributed to the ROI HIPS. Vertices that were active in the calculation localizer (calculation > control) and located anterior to those attributed to the HIPS ROI were defined as aHIPS. The number of vertices that were included in the latter two ROIs were taken as guideline for the size of the subsequent ROIs, when possible [mean = 165.9 vertices (SD = 7.0)]. Based on converging evidence from both human and monkey imaging studies (Culham et al., 2006) the area AIP/BA2 was defined as those vertices that were active in the neutral condition of the landmark task and covered the descending part of the IPS extending to the posterior bank of the postcentral sulcus. This region was chosen since it might correspond to an area in the monkey that was found to contain neurons that code for the number of movements (Sawamura et al., 2002). We chose vertices that were active in the neutral condition to protect us against the circularity fallacy as described by Kriegeskorte et al. (2009). The neutral condition is independent in the sense that those trials did not enter the decoding analyses (see below) but were used only for the selection of the vertices. Active vertices from the saccades localizer that were situated on

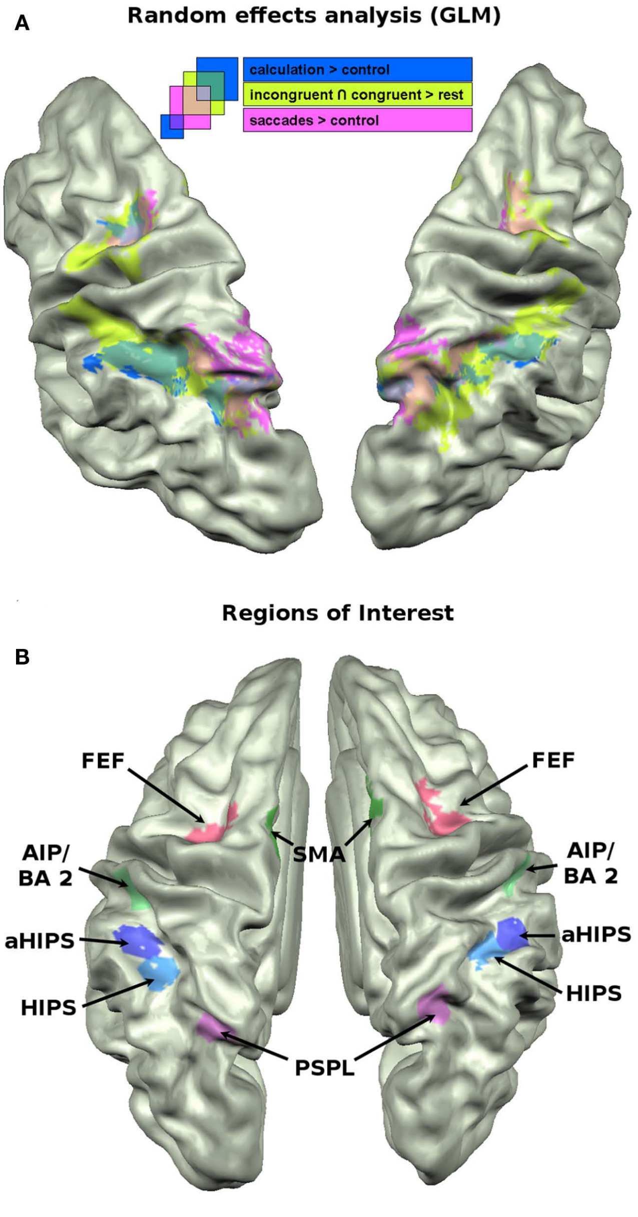

FIGURE 2 | (A) Brain activation data of the GLM analysis ($p = 0.005$) projected on the cortex based aligned average anatomy of the sample. Mapped contrasts: conjunction of incongruent and congruent vs. baseline (green); subtraction vs. control (blue); saccades vs. control (pink). **(B)** The 12 ROIs that were used for across voxel correlations, MVPA, and cluster analyses.

the medial bank of the posterior, superior aspects of the IPS were used to define the PSPL, a putative human homolog of the lateral intraparietal cortex (LIP) region in the monkey (Sereno et al., 2001). For SMA we chose vertices in medial frontal cortex, in close vicinity to the precentral sulcus which were active in the neutral trials of the numerical landmark task. For the FEF we chose vertices that were active in the saccades localizer (saccades > control) and located in precentral sulcus. The ROIs are shown in **Figure 2B**. From these ROIs we extracted the beta weights of the incongruent (I) and congruent (C) conditions of the landmark task, as well as the beta weights from the calculation localizer (A for arithmetic) and the saccades localizer (S). We used the beta weights from the contrasts as described in the GLM analysis (see above). Those beta weights were then correlated across vertices in each of the 12 ROIs as suggested by Peelen et al. (2006). The resulting across-vertex correlation (AVC) matrices reflect the micro-organization of the vertices *within* each of the 12 ROIs in the course of the four cognitive tasks.

To fully explore the differential relations *between* different micro-organizations across vertices in the 12 ROIs we subjected the AVC matrices to a cluster analysis (complete linkage with Euclidean distances as dissimilarity measure) in SPSS software. This cluster analysis reveals the macro-organization of brain activity since it subsumes different ROIs according to their functional similarity in the AVCs at hand.

To investigate the role of each of the above ROIs to the context of numerical–spatial interaction we used MVPA to distinguish between congruent and incongruent number triplets. Unlike other multivariate analysis approaches (e.g., independent component analysis, ICA) that fail to provide quantifiable links to experimental design variables (O'Toole et al., 2007), MVPA is based on the beta weights that are estimated on the basis of the underlying experimental design. Thus, MVPA links the multivariate data analysis to the experimental design and offers a more stringent analysis as compared to other multivariate analysis strategies. Since the rapid event-related design of the current study does not lend itself for the extraction of the raw time series per vertex as input for the MVPA we decided to use the parameter estimates (beta) of a new GLM. We computed the new GLM by defining a predictor for each trial of the landmark task. We focused on the incongruent and congruent trials to exploit the benefits of the bias-free measure from signal detection theory (i.e., d-prime) for the classifier performance. We extracted the betas of incongruent and congruent trials from all vertices in the 12 ROIs defined above, and analyzed them [after z-standardization (mean = 0, SD = 1) per participant and condition over vertices] with a support vector machine (SVM) classifier from the scikits.learn module[1] running on python 2.6[2]. We used a radial basis function kernel (default width = 1/number of features) with a regularization parameter C = 1. Data were cross-validated using a stratified K-fold procedure (K = 64). From each of the two categories (congruent and incongruent) one trial was left out and the classifier was trained on the remaining 126 [$=2 \times (64 - 1)$] trials. The left-out trials were then used to test the generalization of the classifier. Each trial was left out once in a single run, and performance was averaged over 100 runs.

RESULTS

BEHAVIORAL RESULTS

We first analyzed whether behavior (i.e., RT and ER) revealed a significant impact of the congruity between numerical and spatial information.

To this end we calculated a 4 × 5 repeated measures ANOVA with the factors numerical distance (20_80, 40_60,

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[1] http://scikit-learn.sourceforge.net

[2] www.python.org

60_40, and 80_20) and spatial distance (20_80, 40_60, 50_50, 60_40, and 80_20) for RT and ER. Beyond significant main effects of numerical [RT: $F(3,42) = 59.54$, $p < 0.001$; ER: $F(3,42) = 71.41$, $p < 0.001$, $\varepsilon = 0.829$] and spatial distance [only for RT: $F(4,56) = 3.06$, $p < 0.05$] a significant interaction between both factors was observed [RT: $F(12,168) = 8.61$, $p < 0.001$; ER: $F(12,168) = 9.37$, $p < 0.001$, $\varepsilon = 0.796$]. To investigate in more detail the origin of this interaction, we subsumed corresponding conditions under congruent, incongruent, and neutral trials according to the relation of numerical and spatial distances and submitted them to a one-way repeated measures ANOVA with the factor congruity. For RT a significant main effect congruity [$F(2, 28) = 35.75$, $p < 0.001$] was due to increasing mean RT from congruent [1457 ms (270 ms)] over neutral [1515 ms (254 ms)] to incongruent trials [1585 ms (288 ms)]. This order was confirmed by significant *post hoc* paired-sample t-tests [incongruent – congruent: $t(14) = 10.38$, $p < 0.001$; incongruent – neutral: $t(14) = 4.33$, $p = 0.001$; neutral – congruent: $t(14) = 3.49$, $p < 0.01$]. The increase in RT from congruent to incongruent trials was paralleled by a decreasing precision in terms of ER [congruent: 9.4% (5.8%), neutral: 12.9% (7.7%), incongruent: 19.8% (6.5), $F(2, 28) = 28.3$, $p < 0.001$]. *Post hoc* paired-sample t-tests revealed the following order of conditions congruent < neutral < incongruent [incongruent – congruent: $t(14) = 6.81$, $p < 0.001$; incongruent – neutral: $t(14) = 6.46$, $p < 0.001$; neutral – congruent: $t(14) = 2.47$, $p < 0.05$].

BRAIN ACTIVATION DATA

GLM analysis

We begin by summarizing the activated networks of the three administered tasks in a classical GLM approach that are projected on the mean cortex-based aligned brain anatomy of the 15 participants.

The saccade localizer task reliably activated regions in the bilateral posterior parietal cortex, extending into the HIPS, and the FEF in both hemispheres. The results of the contrast saccades > control is shown in pink in **Figure 2A**.

Consistent with results from earlier studies (Pinel and Dehaene, 2010), the calculation localizer (calculation > control) activated bilateral regions along the IPS, extending into posterior parietal areas, partially overlapping with the saccades activations. It also activated portions of the FEF in both hemispheres. The activations are shown in dark blue in **Figure 2A**.

To visualize the cortical network that was activated in the landmark task, we calculated the conjunction of the incongruent and congruent condition against baseline. The numerical landmark task activated a network of areas along the IPS, partially overlapping with the calculation activations and extending into posterior parietal areas where it showed overlap with the saccades task. Unlike these latter two tasks, the landmark task significantly activated regions in more anterior parts of the IPS, i.e., the descending aspect of the IPS including the posterior bank of the postcentral sulcus. Beyond parietal activation it also elicited significant activations in bilateral medial frontal cortex, i.e., SMAs and the FEF overlapping with FEF activation of the previously described tasks. The activations of the landmark task are shown in light green in **Figure 2A**.

To visualize the regions in the brain that are particularly affected by the interaction between numerical and spatial information (see Behavioral Results) we computed the contrast incongruent > congruent trials. No significantly activated region emerged from this contrast, even at a very liberal threshold of $p = 0.05$.

ROI analysis using across-vertex correlations

The beta weights of the incongruent (I) and congruent (C) conditions of the landmark task, as well as the beta weights from the calculation localizer (A for arithmetic) and the saccades localizer (S) were correlated across vertices in each of the 12 ROIs. The resulting AVC matrices reflect the micro-organization of the vertices *within* each of the 12 ROIs in the course of the four cognitive tasks. We subjected the AVC matrices to a cluster analysis (complete linkage with Euclidean distances as dissimilarity measure) to reveal the macro-organization of brain activity.

Results are shown in **Figure 3A**. The height of the AVC in the 12 ROIs is shown as color-coded link between four nodes referring to the activation from the contrast congruent (C, upper left), incongruent (I, lower left), arithmetic (A, upper right), and saccades (S, lower right). Blue and green colors indicate low correlations, followed by yellow, orange for medium, and red for high correlations (see color-bar at the bottom of **Figure 3A**). To facilitate recognition of the different ROIs the colors of the nodes correspond to the colors of the ROIs in **Figure 2B**. Across all 12 ROIs, it becomes evident that congruent and incongruent trials elicit highly correlated patterns of activations ranging from 0.81 in ROI AIP/BA2 of the right hemisphere to 0.94 in ROI PSPL of the right hemisphere. Although the respective patterns of activation across vertices in the different ROIs should be highly correlated, because they are obtained from the same experiment the level of the correlations is remarkably high. Together with the non-significant difference in activation amplitude – as revealed by the contrast incongruent > congruent (see above) – this supports the notion that both types of trials rely on neural circuits that are overlapping in space and show a highly correlated pattern of activity across vertices. It should be noted that the correlation becomes lowest when we move out of parietal cortex and approach response-related motor systems, i.e., ROIs AIP/BA2 and SMA.

The calculation task correlates to a higher degree with the landmark task (irrespective of congruency) than it does with saccades. This makes sense if one keeps in mind that the landmark task entails some calculation aspects in order to determine the larger of the two numerical intervals defined by the number triplet. This relation is even true for areas where calculation elicits only weaker activations and the spatial overlap is hence reduced between all three tasks such as PSPL. Put differently, the correlations across vertices reveal a functional recruitment of certain brain areas in the course of different tasks that would go undetected by the standard GLM approach.

The results of the cluster analysis using all 12 ROIs suggest two large-scale networks. Network one comprises the ROIs SMA_L (the suffixes "_L" and "_R" refer to left and right hemisphere, respectively) and the ROI AIP from both hemispheres and can thus be labeled motor-related network. The second network comprises the remaining nine ROIs and exhibits three sub-clusters. The first

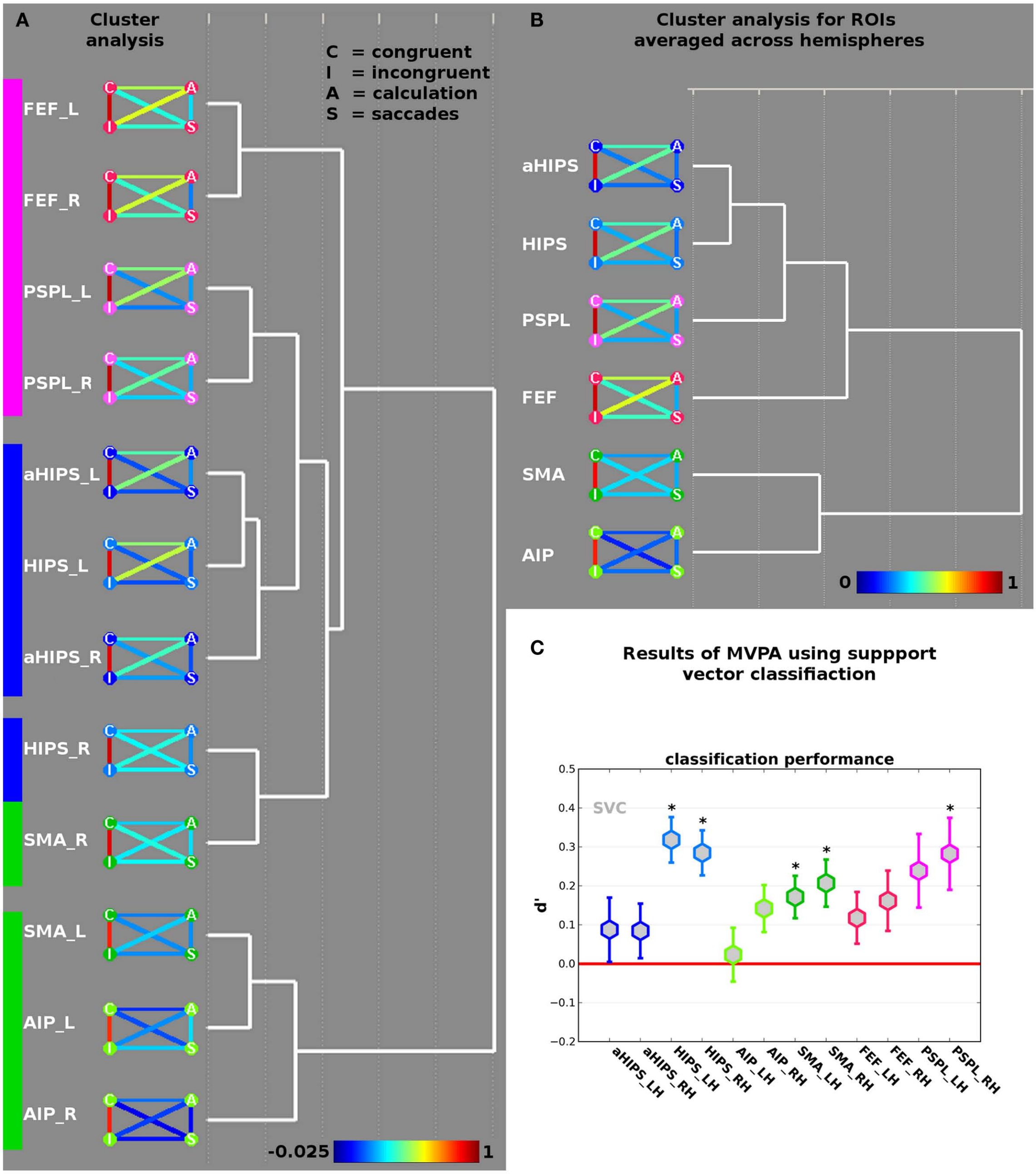

FIGURE 3 | (A) Results of the cluster analysis of the across-voxel correlations between congruent and incongruent contrasts, and the two localizer tasks (saccades and calculation) in the 12 ROIs (see **Figure 2B**). The nodes of the AVC matrices represent congruent ("C"), incongruent ("I"), calculation ("A") and saccades ("S") contrasts. The color of the connecting lines between the disks indicates the height of the respective correlation in the ROI (see bottom for scale). **(B)** Results of the cluster analysis of the 12 ROIs collapsed across hemispheres. **(C)** Results of the decoding analysis differentiating incongruent from congruent trials in the different ROIs. Coefficient d-prime was computed by defining correct classification of congruent trials as congruent as "hit" (true positive) and classification of incongruent trials as incongruent as "correct rejection" (true negative). Stars indicate d-prime significantly larger than zero (red line) at $p < 0.05$ (corrected for multiple comparisons). Error bars represent SE of the mean.

sub-cluster comprises ROIs FEF and PSPL from both hemispheres and can readily be related to eye movements. A second sub-cluster comprises aHIPS from both hemispheres as well as HIPS_L. This sub-cluster cluster can be related to number processing and calculation. A third sub-cluster contains only two ROIs from the right hemisphere, i.e., HIPS_R and SMA_R. This sub-cluster might represent ROIs that link motor-related regions with number processing and saccades.

We further analyzed the macro-organization by collapsing ROIs over hemispheres and submitting the averaged correlation matrices to the same cluster algorithm (complete linkage with Euclidean distances). The result is shown in **Figure 3B**. Again, we find a motor-cluster comprising the ROIs AIP and SMA, as well as a second cluster with a core sub-cluster comprising the number-related ROIs (HIPS and aHIPS). Only in subsequent iterations ROIs from the saccades system (i.e., FEF and PSPL) are assigned to the cluster, implying that, averaged across hemispheres, HIPS is more similar to aHIPS than to SMA.

The analysis of the micro and macro-organization of the different tasks in the different ROIs can be interpreted as first evidence for a subdivision of the areas along the HIPS and a differential involvement of the areas defined here in the resolution of the conflict occurring when spatial and numerical information do not converge on the same response. Broadly speaking, we find that the cluster analysis differentiates the motor system (SMA & AIP/BA 2) from the saccades & number system. On a more fine-grained level we see that the ROIs HIPS and SMA of the right hemisphere seem to be functionally located in between the two large-scale clusters. This implies that the HIPS of left and right hemisphere seem to serve slightly different purposes, with the HIPS_L being more closely related to the other areas from the HIPS, i.e., putatively number-related areas (aHIPS). Right hemisphere HIPS seems to be closely related to the motor system since it clusters with SMA of the right hemisphere. Inversely one might argue that the SMA of the right hemisphere seems to be linked with number-related processes as clusters with right hemisphere HIPS.

Multi vertex pattern analysis

To further investigate the implication of the different clusters (and the ROIs therein) in the context of the numerical landmark task we used a SVM classifier to differentiate congruent from incongruent trials. Similar to the correlations across vertices reported above, MVPA takes into account the spatial relations between vertices in a given ROI and goes beyond the vertex-wise analysis approach of the GLM that treats vertices as independent from each other.

Results are shown in **Figure 3C**. Stars indicate significant classification performance ($p < 0.05$) as tested by a one-sample t-test against zero, corrected for multiple comparisons (see Materials and Methods section). We observed a d-prime significantly larger than zero in the ROIs HIPS_L [$d' = 0.32$, $t(14) = 5.29$, $p = 0.0001$], HIPS_R [$d' = 0.28$, $t(14) = 4.76$, $p = 0.0003$], SMA_R [$d' = 0.21$, $t(14) = 3.31$, $p = 0.005$], SMA_L [$d' = 0.17$, $t(14) = 3.05$, $p = 0.009$], and PSPL_R [$d' = 0.28$, $t(14) = 2.95$, $p = 0.011$]. It should be noted that classification performance in PSPL_L and right hemisphere AIP/BA 2 was good but did not pass the statistical correction for multiple testing [$d' = 0.24$, $t(14) = 2.44$, $p = 0.028$ and $d' = 0.14$, $t(14) = 2.27$, $p = 0.039$, respectively]. It becomes evident that in individual ROIs from each of the two large-scale networks, which were identified and described above, the spatial activation patterns allowed for a better-than-chance distinction between congruent and incongruent trials. Overall, classification performance was best in parietal areas with classification rates in terms of d' up to 0.32 in left HIPS. To test for putatively different classification results between the different ROIs we computed a 2 × 6 repeated measures ANOVA with the factors hemisphere (2) and ROI (6) on the individual d-prime measures. We observed a significant effect of ROI [$F(5,70) = 3.29$, $p = 0.017$, $\varepsilon = 0.8$]. No other main effect or interaction was significant (all $F < 1$). We ran pair wise comparisons between the ROIs averaged across hemispheres and found that d-prime in HIPS was significantly higher than in aHIPS [$t(14) = 4.04$; $p = 0.001$]. No other pair wise comparisons were significant after correction for multiple comparisons. Since the ANOVA suggests that hemisphere does not have a significant impact on the data, we re-analyzed the individual d-primes from the six ROIs and found d-primes significantly larger than zero in HIPS [$t(14) = 5.87$ and $p < 0.0001$], SMA [$t(14) = 4.07$, $p = 0.001$], and PSPL [$t(14) = 3.34$ and $p = 0.005$].

To avoid possible confounds in the classification we checked if participants pressed as much left as right for both incongruent and congruent trials in the landmark task by computing a 2 × 2 repeated measures ANOVA with the factors “side” and “congruency” on the frequency of left and right button presses under the two conditions. We observed a significant main effect of congruency [$F(1,14) = 6.472$, $p = 0.023$, $\varepsilon = 1$]. No other main effect or interaction was significant (all $p > 0.05$). In none of the two congruency conditions (congruent or incongruent) we observed a significant difference in frequency of left vs. right button presses [congruent: $t(14) = 0.4706$, $p = 0.645$; incongruent: $t(14) = 1.8522$, $p = 0.085$].

DISCUSSION

The present study was designed to investigate the interaction between numbers and space and its neural correlates with a focus on parietal cortex. By doing so we hoped to be able to separate early from late interaction of both dimensions. Behaviorally, we found that congruent number triplets were responded to faster and more accurately than neutral and incongruent number triplets. Together with an absence of the corresponding interaction when participants had to respond to the *spatial* intervals (Knops et al., submitted) this suggests that spatial and numerical information are extracted and processed in parallel and independent routes that interact at the level of response selection/response preparation only. The present study is the first to employ a comprehensive analysis of both the micro- and macro-patterns of brain activation in a task tapping numerical–spatial interaction and complementing standard massive univariate analysis techniques by model-related, multivariate analysis techniques (i.e., MVPA and AVC). For the numerical landmark task the standard GLM approach revealed activation in a network including regions along the IPS, areas in central and postcentral sulcus as well as supplementary motor cortex, and FEF. Activation overlapped with activation from the calculation localizer in HIPS, PSPL, and FEF (see **Figure 2A**). In PSPL and FEF we found an overlap between the saccades network and the numerical landmark task. By clustering the patterns of the correlations across vertices, we were able to identify two independent large-scale networks, each encompassing several ROIs. The networks can readily be described as a motor or response-related network comprising regions AIP/BA 2 and SMA as opposed to a saccades & number network, comprising the remaining ROIs. Within the latter cluster we observed three sub-clusters that can be labeled as a saccades network (FEF and PSPL), a number network (aHIPS and HIPS_L), as well as a right hemispheric network that links number and motor processes (HIPS_R and SMA_R). At first, the appearance of right hemisphere ROIs HIPS and SMA in a sub-cluster seemed somewhat surprising, given that SMA is frequently linked with response selection while the HIPS has repeatedly been shown to subserve number representation and mental arithmetic (Piazza et al., 2004, 2007; Hubbard et al., 2005). Apart from numerical functions the HIPS seems to serve manifold purposes, however. Most central to the present study, some authors argue that regions in the IPS that most likely corresponds to our ROI HIPS are implicated in response selection processes (Jiang and Kanwisher, 2003a,b) while more recent studies investigating the locus of response selection suggest more frontal areas such as posterior lateral prefrontal cortex (pLPFC) and SMA (Dux et al., 2006). Dux et al. (2006) argue that some aspects of the IPS activity profile support its implication in response selection processes, while other aspects make it appear a more general purpose area. Here the current approach might help to further specify the cognitive functions of a given area. Rather than focusing on the signal variation in a single spot, we also take into account the spatial variation of the signal and its relation with other regions in the brain. The results of the cluster analysis imply differential involvement of sub-regions along the IPS. While left hemisphere ROIs HIPS and aHIPS seem to be clearly distinct from the response-related system, the right HIPS appears to be functionally involved in both – numerical and response-related processes. Our study is thus one of the first to delineate in greater detail a putative candidate network in the right hemisphere that links numerical and response-related processes in the course of a task that shows a massive interaction between numerical and spatial information.

Although the temporal resolution of fMRI does not allow for a clear-cut distinction between input and output-related processes, the different networks can be attributed to stages of information processing in the course of the current task. One might then analyze activation data from these regions to investigate different stages of information processing.

In case of early interaction, numerical and spatial information should be integrated before further processing. Since both, numerical and spatial information, are processed in parietal cortex we hypothesized that parietal cortex would qualify as a candidate area for the integration of spatial and numerical information. This is in line with Walsh (2003) who assumed common metrics for numbers, space, and time that have their neural correlates in parietal cortex and with the finding of Tudusciuc and Nieder (2009), who observed neurons in parietal cortex that simultaneously coded for numerical and spatial features of a stimulus. We further reasoned that if the integration is accomplished in parietal cortex, we should observe differences between congruent and incongruent trials in exactly those regions. While the GLM analysis did not reveal any significant difference between incongruent and congruent trials, by adopting a MVPA analysis we were able to identify regions in the HIPS in which both types of trials evoked separable spatial patterns of activation. The fact that we were able to classify congruent from incongruent trials in ROIs that – as revealed by the cluster analysis – can be coined a number-related network speaks for an early interaction between both stimulus dimensions.

The late interaction notion posits that numerical and spatial information are extracted and processed in parallel and interact only at the level of response selection/response preparation. We hypothesized that in this case we should be able to classify congruent from incongruent trials in a response-related network in the brain. The cluster analysis revealed a response-related network consisting of SMA_L and AIP/BA2. According to the cluster analysis this network is functionally maximally different from the other ROIs since they are agglomerated only at the last linkage level (see **Figures 3A,B**). The MVPA analysis revealed a better-than-chance classification performance between congruent and incongruent trials in left and right SMA (see **Figure 3C**). This constellation can be interpreted in at least two ways. First, the differential activation pattern can be interpreted as a consequence of an inhibition process that operates in incongruent trials when irrelevant spatial response tendencies have to be suppressed but less so in congruent trials when no response tendency has to be inhibited. In this vein Forstmann et al. (2008) recently observed a strong link between both functional and structural fMRI parameters in right ventral premotor cortex and RT parameters that signal response inhibition in a Simon task. The ventral premotor cortex, in turn, is predominantly interconnected with the region AIP (Rushworth et al., 2006), a region that showed good albeit not significant classification performance in the right hemisphere. Second, these differential activation patterns could represent a direct consequence of the differential activation patterns in the number-related network, i.e., these regions receive their input from the close-by number-related network (aHIPS and HIPS_L) and covary with the latter. This is further corroborated by the finding that HIPS_R and SMA_R cluster form a sub-cluster that might link number and motor information in the course of information processing. On the basis of the present data we cannot decide between these two interpretations. Most crucially, both imply a significant contribution of the response-related network which in turn lends support to late interaction between numbers and space.

A major advantage of the adopted CBA in combination with unsmoothed imaging data of higher accuracy is that we can delineate in higher detail the neuro-cognitive architecture in tasks tapping number space interaction. In combination with the MVPA analyses we found that some parietal regions are differentially involved in congruent and incongruent trials (e.g., PSPL, HIPS) while others are not. In particular we could demonstrate that aHIPS is well activated by the numerical landmark task (and the calculation localizer) but its contribution appears unaffected by the congruency between numerical and spatial information. One might speculate that aHIPS is implicated in "purely" numerical processes of a task, i.e., it remains unaffected by its spatial aspects. In contrast, it has been argued that area hIP2 but not area hIP1, two anterior areas in the IPS where hIP2 may roughly correspond to our ROI aHIPS while hIP1 may overlap with our ROI HIPS (Choi et al., 2006), was implicated in "top-down modulated directionality-specific reorienting of motor attention during incongruent motor responses" (Cieslik et al., 2010). With the present study we cannot disentangle numeric processes from more general task components or top-down processes in manual response tasks, unfortunately. This demonstrates the importance of increased spatial resolution in future neuroimaging studies to further improve the mapping of numerical and spatial functions along the IPS.

The successful classification performance in the eye movement network (PSPL) may reflect differential scanning patterns in congruent and incongruent trials, respectively. This result cannot be explained in terms of a simple difference in amplitudes of the BOLD response, e.g., due to more eye movements in incongruent than in congruent trials for two reasons. First, as reported above, there was no region that showed a significant difference in terms of amplitude of the BOLD response. Second, before entering the beta weights from each of the two conditions into the classifier they were z-standardized, thus leveling out putative differences in amplitude.

Taken together, the results are in line with the literature that reports evidence for an integrated representation of several dimensions, amongst them numbers and space (Schwarz and Heinze, 1998; Walsh, 2003). The results are also in line with evidence for a late interaction of information in tasks that induce a conflict between irrelevant and relevant stimulus dimensions (Ridderinkhof, 2002; Cohen Kadosh et al., 2007, 2008; Forstmann et al., 2008).

By combining the AVC with a cluster analysis we identified two functional networks devoted to sensory–motor information on the one side and eye movements and number processing on the other with the latter containing three sub-cluster devoted to eye movements, number processing, and linking number to motor information, respectively. While the eye movement system is strictly organized according to ROIs (i.e., ROIs are clustered across hemispheres), this is not the case for the remaining clusters that combine ROIs from within one hemisphere on the first clustering level (e.g., aHIPS_L and HIPS_L for number system). Additionally, it should be noted that the cluster analyses do not merely reflect superficial task characteristics, such as whether mental manipulation of numbers is required or not. In this case, the eye movement system would be different from a second cluster containing all other ROIs. This is clearly not the case. This demonstrates that the results of this analysis are far from trivial and that the presented combination of AVC and cluster analysis might prove useful in identifying large-scale functional networks in many domains of cognitive neuroscience. It may serve the definition of functionally defined regions of interest that can then be subject to further analyses. By carefully adapting tasks and contrasts in a given study it might prove useful to investigate to what degree the large-scale organization of brain activity reflects participants' different performance levels. Rotzer et al. (2009), for instance, suggested that a dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. The combination of AVC and cluster analysis might be used to delineate the functional relation between these networks and other related functions such as different aspects of verbal working memory or memory retrieval in both dyscalculics and controls.

To sum up, by enriching standard GLM analysis with a combination of AVC and cluster analysis we identified large-scale networks that can be related to different stages of information processing. In each of these we were able to differentiate congruent from incongruent trials by using support vector classification. We provide evidence for both an early integration and a late interaction of conflicting stimulus dimensions, i.e., numerical and spatial distances.

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Optokinetic stimulation modulates neglect for the number space: evidence from mental number interval bisection

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Behavioral, neuropsychological, and neuroimaging data support the idea that numbers are represented along a mental number line (MNL), an analogical, visuospatial representation of number magnitude. The MNL is left-to-right oriented in Western cultures, with small numbers on the left and larger numbers on the right. Left neglect patients are impaired in the mental bisection of numerical intervals, with a bias toward larger numbers that are relatively to the right on the MNL. In the present study we investigated the effects of optokinetic stimulation (OKS) – a technique inducing visuospatial attention shifts by means of activation of the optokinetic nystagmus – on number interval bisection. One patient with left neglect following right-hemisphere stroke (BG) and four control patients with right-hemisphere damage, but without neglect, performed the number interval bisection task in three conditions of OKS: static, leftward, and rightward. In the static condition, BG misbisected to the right of the true midpoint. BG misbisected to the left following leftward OKS, and again to the right of the midpoint following rightward OKS. Moreover, the variability of BG's performance was smaller following both leftward and rightward OKS, suggesting that the attentional bias induced by OKS reduced the "indifference zone" that is thought to underlie the length effect reported in bisection tasks. We argue that shifts of visuospatial attention, induced by OKS, may affect number interval bisection, thereby revealing an interaction between the processing of the perceptual space and the processing of the number space.

Keywords: mental number line, neglect, pseudoneglect, optokinetic stimulation, spatial attention, number processing, bisection, nystagmus

INTRODUCTION

Number processing is a fundamental skill for everyday living. Indeed, numbers are necessary for many basic activities such as achieving financial interactions and management, telling the time, selecting the correct bus, making a phone call, performing scientific measurements, and so on. Thus, a brain without numbers could make little sense of its internal and external environment, given that various and important everyday activities involving processing of numbers should be compromised (see Dehaene, 1997; Butterworth, 1999, for comprehensive reviews).

An essential question is how knowledge of number is represented in the brain. How, for example, can we decide quickly and effortlessly which of two numerals expresses the greater magnitude or which of two sets contains the smaller number of elements? This has been an important challenge for cognitive neuroscientists during the last decades and encouraging theoretical proposals have been formulated on various empirical grounds. Indeed, recent research on numerical processing in animals and humans converge on the view that knowledge of numbers constitutes a domain-specific cognitive ability, with a specific neural substrate located in the left and right inferior parietal cortices (see Dehaene et al., 2003).

A far more complex issue, however, is that of the nature of these representations. Dehaene and Cohen (1995) have proposed a comprehensive cognitive–anatomical model to explain various aspects of mathematical cognition. In this model, mathematical information is represented by three distinct codes: an Arabic code, a verbal code, and a code consisting in a continuous, analogical left-to-right oriented mental number line (MNL), where small numbers are represented on the left and progressively larger numbers are represented on the right. According to Dehaene and Cohen (1995), the three codes have different representational and functional properties. The first two codes, for example, are notation-dependent (Arabic vs. verbal). More precisely, the verbal code is responsible for the recognition and production of number words (spoken and written), for the retrieval of rote-memorized arithmetic facts (e.g., the multiplication table, the results of frequent one-digit additions and subtractions, etc.), and for counting. The Arabic code is implicated in the recognition and production of Arabic digits, in parity judgment (i.e., decide if a number is odd or even), and in multi-digit written calculations. The third code (the MNL), in contrast, is supramodal (i.e., notation-independent) and, thus, it can be activated both by numerals (Arabic digits, spoken number words, written number words, etc.) and by directly perceived numerosities of distinct elements in the environment (objects, people, animals, etc.). The principal role of the MNL is to represent the meaning both of numerals and of perceived numerosities by translating them into a continuous and analogical magnitude code (Dehaene et al., 2003). Thus, the MNL supports number comparison (e.g., "is 5 bigger than 6?") and approximate calculation (e.g., "does the operation $3 + 4$ equals 15?").

It has been shown that each of these codes has a specific cerebral localization (Dehaene and Cohen, 1995). More precisely, the Arabic code is implemented in the inferior mesial occipital–temporal cortices bilaterally, whereas the perisylvian circuits of the left hemisphere support the verbal code. Finally, the analogical code is subserved by the inferior parietal cortices bilaterally. The three codes are coordinated by general-purpose executive systems localized in the prefrontal cortices bilaterally (Dehaene and Cohen, 1995; Dehaene et al., 2003).

Although the notion of MNL is widely accepted in the numerical cognition literature, what remains controversial is whether the MNL has a truly spatial nature (for reviews, see Dehaene et al., 2003; Hubbard et al., 2005; Umiltà et al., 2009). Dehaene et al. (1990) were the first to report experimental evidence in favor of the spatial format of the MNL. In their study, participants were asked to decide, by pressing either a right-sided or a left-sided key, whether Arabic digits displayed at fixation were larger or smaller than a fixed reference number (i.e., 65). Although key order was counterbalanced, Dehaene et al. (1990) observed that participants were more efficient in pressing the left-sided key for responding "smaller" (Arabic digits <65) and the right-sided key for responding "larger" (Arabic digits >65). Hence, there seemed to be an effect of spatial correspondence between the effector of the response and the position of the processed number on the MNL (i.e., left or right with respect to the reference number). In a second study, Dehaene et al. (1993) observed that there was a left-sided key advantage for small numbers and a right-sided key advantage for larger numbers, even in a task that did not require direct manipulation of number magnitude. In this study, participants were presented with centrally displayed Arabic digits, and they were asked to perform parity judgments by pressing a left-sided or a right-sided key. The results revealed that participants were significantly faster and more accurate in responding to relatively small numbers with their left hand, whereas they were more accurate and fast in responding to relatively large numbers with their right hand. This correspondence between the position of a number on the MNL and the spatial position in which the response to that number took place was termed the spatial numerical association of response codes (SNARC) effect.

The SNARC effect, however, might be also explained by other recent theories that dispense with the spatial coding of numbers (see Gevers et al., 2006; Proctor and Cho, 2006). For example, Gevers et al. (2006) developed a computational account of the SNARC effect, in which "a specific number is not coded as left or right but (. . .) is coded as either small or large, which in turn activates left or right responses." The account of Proctor and Cho (2006; see also Santens and Gevers, 2008) is based on the idea that stimuli and associated responses in binary choice tasks are coded with positive and negative polarities. Proctor and Cho (2006) suggested that the SNARC effect may be the result of coding large numbers as positive and small numbers as negative, which would then produce match or mismatch with the polarity coding of responses (negative for left and positive for right). We think, however, that the notion of polarity correspondence does not run against the notion of a spatial representation of numbers. The minus ($-$) and plus ($+$) signs are systematically associated with Cartesian coordinates in order to represent spatial positions to the left ($-$) or to the right ($+$) of a reference point (i.e., zero). Kosslyn (1994, for review) has proposed a dual system for coding space in the human brain: coordinate spatial codes (e.g., Cartesian coordinates), implemented in the right hemisphere, and categorical spatial codes (e.g., left, right, above, below, etc.), implemented in the left hemisphere. Thus, polarity correspondence might simply involve Kosslyn's categorical spatial coding. Nevertheless, the graded nature of the SNARC effect (i.e., a linear progression from left-sided response advantage to right-sided response advantage as magnitude increases; e.g., Fias et al., 1996; Priftis et al., 2006) cannot be explained if coding were only categorical.

Further evidence in favor of the spatial format of the MNL has been reported in studies on neurological patients. Zorzi et al. (2002) investigated whether the MNL has a left-to-right spatial organization, by exploring the way numbers are represented in patients affected by left neglect. These patients, more frequently following a right parietal lesion, fail to report, orient to, or verbally describe stimuli in the contralesional side of space (i.e., the left side; for review, see Halligan et al., 2003). When neglect patients are asked to bisect physical lines, they systematically misbisect to the right of the true midpoint of the line, as if they were ignoring its leftmost part. Halligan and Marshall (1988; also see Marshall and Halligan, 1989) observed that this rightward misbisection is directly proportional to the length of the physical line. That is, the longer the physical line, the greater the misbisection to the right of the true midpoint, although leftward misbisection was observed for very short physical lines (i.e., the "crossover" effect).

To investigate whether the MNL has spatial features similar to those of physical lines, Zorzi et al. (2002) asked left neglect patients to mentally bisect numerical intervals (e.g., "Which number is halfway between 1 and 9?"). The results showed that left neglect patients misbisected to the "right" of the true midpoint of longer number intervals (e.g., responding that "7" is halfway between "1" and "9"), but they misbisected to the left of the true midpoint of shorter number intervals (e.g., responding that "6" is halfway between "7" and "9"). Thus, the overall pattern observed in mental number interval bisection resembled that of left neglect patients during the bisection of physical lines. The findings of Zorzi et al. (2002) have been replicated and extended in a number of recent studies reporting effects of neglect on number processing (Rossetti et al., 2004; Vuilleumier et al., 2004; Doricchi et al., 2005; Priftis et al., 2006, 2008; Zorzi et al., 2006; Cappelletti et al., 2007; Zamarian et al., 2007; Hoeckner et al., 2008; Loftus et al., 2008; Yang et al., 2009; for review see Umiltà et al., 2009). The converse relation has been also reported; that is, number processing can modulate left neglect. Bonato et al. (2008) have reported that the presence of small numbers ameliorates physical line bisection in left neglect patients. Loftus et al. (2008) have shown that processing of small numbers overcomes left neglect in a perceptual task. Finally, a reliable "leftward" bias (i.e., "pseudoneglect") has been reported in healthy participants engaged in various numerical tasks (Longo and Lourenco, 2007; for review, see Umiltà et al., 2009). This bias mirrors, in the number space, the well-known asymmetries observed when healthy participants deploy their visuospatial attention in the physical space (for a review on pseudoneglect in physical space, see Jewell and McCourt, 2000).

Nevertheless, in a recent paper reporting the case study of a patient with right-sided neglect following left hemisphere damage, van Dijck et al. (2011) have proposed that the misbisection pattern observed in neglect patients during number interval bisection is due to a deficit in processing the initial items in a sequence to be held in verbal working memory, rather than a consequence of neglect (also see Fias et al., 2011, for review). If this were the case, one would expect that manipulation of spatial variables should not affect neglect for the number space, given that these manipulations do not affect verbal working memory. There are two published studies that are difficult to reconcile with the verbal working memory account. First, Rossetti et al. (2004) showed that the overall rightward bias of left neglect patients in bisecting mental number intervals can be ameliorated following adaptation to rightward-shifting prisms, a well-known and widely used technique for rehabilitating visuospatial attention deficits of neglect patients. Second, Salillas et al. (2009) reported that leftward, coherent dot movement can improve the difficulties of left neglect patients in judging the magnitude of numbers, which are smaller (e.g., 4) than a reference number (e.g., 5). Note that this task is minimally based on verbal working memory resources, because participants must remember only one item (i.e., the reference number) for performing the task.

The aim of the present study was to investigate whether optokinetic stimulation (OKS) – a technique inducing visuospatial attention shifts by means of elicitation of the optokinetic nystagmus (for review, see Kerkhoff, 2003) – would influence mental number interval bisection in a way similar to the way OKS affects physical line bisection. Indeed, Pizzamiglio et al. (1990) have shown that, with respect to a static OKS condition, leftward OKS improves physical line bisection, whereas rightward OKS deteriorates physical line bisection. Pizzamiglio et al. (1990) showed that these effects were particularly strong and evident in neglect patients with respect to controls. We tested one left neglect patient (BG) and four right-hemisphere damaged control patients without neglect. We postulated that if a deficit in verbal working memory was the reason underlying number interval misbisection, then OKS should have no effects on the performance of the left neglect patient. In contrast, if neglect was the core deficit, leftward OKS should improve number interval bisection, whereas rightward OKS should deteriorate it. Finally, in contrast with Salillas et al. (2009) who used coherent dot motion, in the present study OKS consisted in fast-moving vertical stripes, a visuosensory manipulation which elicits the optokinetic nystagmus (see below).

MATERIALS AND METHOD

CASE DESCRIPTION

BG, a 64-year-old, right-handed man with 4 years of education, suffered a right-hemisphere ischemic stroke. He had negative neurological and psychiatric history. A computed tomography (CT) scan, performed immediately after his stroke, evidenced a hypodense area in the temporo-parietal region of the right cerebral hemisphere that was extended subcortically to the ventricular-thalamic regions. A second CT scan revealed an extensive hypodense right cerebral lesion accompanied by non-homogeneous, paraventricular-thalamic areas of hypodensity; median structures were in axis. Another CT scan reconfirmed the presence of the same hypodense areas. During hospitalization, BG was complied with physical therapy for left body hemiparesis and neuropharmacological treatment. At the moment of testing, BG was able to take short walks with the help of a tripod, but he mainly used the wheelchair to move himself.

Table 1 | Demographic, clinical, and psychometric data of the participants.

	BG	SL	BGA	CP	CL
Sex	M	FE	M	M	M
Age (years)	64	55	71	72	54
Education (years)	4	8	5	18	10
Handedness	R	R	R	R	R
Lesion site	TPThPv	FTP	FP	BN	Th
Lesion etiology	IS	IS	IS	HS	IS
MMSE	23.4/30	30/30	28.3/30	30/30	24/30
BIT CONVENTIONAL SUBTESTS					
Line crossing	36/36	36/36	36/36	36/36	36/36
Letter cancelation	11/40	40/40	36/40	40/40	38/40
Star cancelation	40/54	54/54	54/54	53/54	54/54
Figure copy	0/3	2/3	2/3	3/3	2/3
Shape copy	1/1	1/1	1/1	1/1	1/1
Line bisection	6/9	9/9	9/9	9/9	9/9
Spontaneous drawing	1/3	1/3	0/3	2/3	1/3
Total score	95/146	143/146	138/146	144/146	141/146

M, male; FE, female; MCA, middle cerebral artery territory; F, frontal; T, temporal; P, parietal; Th, thalamic; Pv, paraventricular; BN, basal nuclei; R, right; IS, ischemic stroke; HS, hemorrhagic stroke.

BG underwent formal neuropsychological evaluation. He was alert and collaborative, and oriented to personal information, even if he was only partially oriented in time and space. He had no memory or communication difficulties in everyday life, despite his hypoacusia, which was present even before his stroke. His social, behavioral, and emotional control remained well adapted. Clinical signs of left neglect, consisting in spontaneous head and gaze deviation toward the ipsilesional hemispace, were present. His score on the conventional part of the Behavioral Inattention Test (BIT; Wilson et al., 1987) was below the cut-off, revealing that BG was affected by left neglect. BG gave his informed consent in order to participate in the study, according to the Declaration of Helsinki. Demographic, clinical, and psychometric data of BG are reported in **Table 1**.

RIGHT-HEMISPHERE DAMAGED CONTROL PATIENTS

Four patients (SL, BGA, CP, CL; mean age 63 years, SD 9.83, mean education 10.25 years, SD 5.56) with right-hemisphere stroke, but without left neglect (hereafter RBDN-group) took part in the study, after giving their informed consent according to the Declaration of Helsinki. Inclusion criteria comprised absence of dementia, substance abuse, and psychiatric disorders. Left neglect was assessed through the conventional part of the BIT (Wilson et al., 1987): all control patients obtained a score above the cut-off

Table 2 | The complete set of number intervals.

Length	Units	Teens	Twenties
3	1–3, 2–4, 3–5, 4–6, 5–7, 6–8, 7–9	11–13, 12–14, 13–15, 14–16, 15–17, 16–18, 17–19	21–23, 22–24, 23–25, 24–26, 25–27, 26–28, 27–29
5	1–5, 2–6, 3–7, 4–8,5–9	11–15, 12–16, 13–17, 14–18, 15–19	21–25, 22–26, 23–27, 24–28, 25–29
7	1–7, 2–8, 3–9	11–17, 12–18, 13–19	21–27, 22–28, 23–29
9	1–9	11–19	21–29
Total	16	16	16

(129/146). The MMSE (Magni et al., 1996) was also administered to exclude the presence of general cognitive impairments. Demographic, clinical, and psychometric data of control patients are reported in **Table 1**.

MENTAL NUMBER INTERVAL BISECTION TASK

Stimuli

Stimuli and procedure were the same as those used by Zorzi et al. (2002; see also Priftis et al., 2006). Forty-eight forward (e.g., 1–9) and 48 backward (e.g., 9–1) number pairs were orally presented to the participants. Each trial was presented once, in random order. Each number pair defined a specific number interval, whose length was three (e.g., 1–3), five (e.g., 1–5), seven (e.g., 1–7), or nine (e.g., 1–9). Each number interval was presented within the units (e.g., 1–5), the teens (e.g., 11–15), and the twenties (e.g., 21–25). The complete set of number pairs is reported in **Table 2**.

OPTOKINETIC STIMULATION

Stimuli

Optokinetic stimulation consisted of moving white vertical stripes (width: 1 cm, height: 11.5 cm, luminance: ~76 cd/m^2), presented against a black background (luminance: 0.42 cd/m^2) at the speed of 8.4 cm/s. The inter-stripe distance was 1 cm.

APPARATUS AND PROCEDURE

A notebook (Intel® Pentium® M, CPU: 1.86 GHz, RAM: 512 MB, graphics card: 128 MB, 15″ screen, refresh rate: 60 Hz, 32 bit colors, 1400 × 1050 pixel resolution) was used to display the OKS. All participants were tested in the same room and under the same luminance condition. The experiment was composed by a preliminary session followed by an experimental session. In the preliminary session, participants sat in front of the screen. A chinrest was used to keep the eyes of the participants at a distance of 40 cm from the screen. Participants were asked to fixate the center of the screen while either leftward or rightward OKS was presented. All participants had normal optokinetic nystagmus, characterized by a slow phase of eye movement toward the direction of the OKS and a rapid phase opposite the direction of the OKS. In the experimental session, participants remained positioned in front of the screen, with their head fixed in the chinrest. Participants were asked to look at the center of the screen. The experimenter sat behind the screen out of the participants' view and controlled, using a camcorder, whether the participants showed the nystagmus and whether they maintained their gaze on the screen. During the presentation of the OKS conditions (static, leftward, rightward), participants were presented with spoken number pairs and they were asked to say aloud which number was halfway between the first and the second number of each pair (e.g., the experimenter asked: "What number is halfway between 1 and 9?"). There was no time limit for the participants to perform the task. The number pairs were repeated to the participants whenever required. OKS was presented to the participants in three separate blocks (static, leftward, rightward) in three consecutive days (one block on each day).

RESULTS

For each participant and for each number interval, the mean difference between observed (O) and correct (C) responses (dO–C) was calculated (see **Table 3**). For each participant and condition, responses above and below 3 SD from the mean were excluded from the statistical analyses. The resulting number of outliers was very small (BG: static 2.83%, leftward 2.83%, rightward 0%; RBDN: static 0.26%, leftward 2.08%, rightward: 0.78%).

For each participant and each condition of OKS (static, leftward, rightward), Pearson's r coefficients were calculated (number interval length vs. dO–C). We used specific tests for comparing the Pearson's r coefficient of BG with those of the RBDN-group (Crawford et al., 2003). In the static condition (see **Figure 1**), BG misbisected significantly to the right of the true midpoint ($r = 0.25$), as a function of number interval length, $t(3) = 3.527$, dO–C = 0.019, one-tailed, showing the typical pattern of mental number interval bisection observed in left neglect patients. Leftward OKS (see **Figure 2**) improved the performance of BG, which became not significantly different ($r = 0.07$) from that of RBDN-controls, $t(3) = 0.271$, $p = 0.402$, one-tailed. Finally, rightward OKS (see **Figure 3**) induced BG to misbisect again to the right of the true midpoint, as a function of number interval (BG: $r = 0.41$), $t(3) = 2.551$, $p = 0.042$, one-tailed.

Leftward and rightward OKS appeared to induce a reduction of the SE in BG (SE across interval lengths = static: 1.323, leftward: 0.736, rightward: 0.321; also see **Figures 1–3**). Therefore, we performed further analyses to assess whether the change in variability in BG's performance, as a function of OKS condition, was different from that of controls. To this aim we used the revised standardized difference test (Crawford and Garthwaite, 2005), which is designed to test the difference of a patient's performance in two conditions, with respect to that of controls. With respect to the static condition, both leftward and rightward OKS decreased BG's SE [static vs. leftward OKS, $t(3) = 19.049$, $p = 0.0003$, two-tailed; static vs. leftward OKS, $t(3) = 15.386$, $p = 0.0006$, two-tailed]. Finally, BG's SE was smaller in the rightward than in the leftward OKS condition, $t(3) = 8.831$, $p = 0.0003$.

DISCUSSION

BG, a left neglect patient, misbisected to the right of the true midpoint of number intervals. His performance significantly improved following leftward OKS given that it became indistinguishable from that of control patients. BG misbisected again to the right of the true midpoint of the number intervals following rightward OKS. Although it may appear that rightward

Table 3 | For each participant the mean dO–C and the associated SE is reported, as a function of number interval length and OKS.

Length	3		5		7		9	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
STATIC OKS								
Patient BG	0.049	0.324	0.133	0.266	1.118	0.624	3.667	4.080
RBDN-1	0.000	0.000	−0.167	0.097	−0.222	0.173	0.167	0.307
RBDN-2	0.000	0.000	0.000	0.000	0.056	0.151	−0.500	0.224
RBDN-3	0.000	0.000	0.000	0.000	0.000	0.081	−0.333	0.211
RBDN-4	0.000	0.000	−0.133	0.063	−0.111	0.137	−0.667	0.211
LEFTWARD OKS								
Patient BG	0.317	0.417	0.233	0.257	0.471	0.550	1.167	1.721
RBDN-1	0.000	0.000	−0.033	0.102	−0.056	0.235	1.000	0.365
RBDN-2	0.000	0.000	0.000	0.000	−0.056	0.171	0.000	0.258
RBDN-3	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
RBDN-4	0.000	0.000	−0.103	0.076	−0.278	0.195	0.333	0.422
RIGHTWARD OKS								
Patient BG	0.095	0.243	0.400	0.265	0.667	0.443	3.333	0.333
RBDN-1	0.000	0.000	0.000	0.096	−0.167	0.167	0.500	0.500
RBDN-2	0.000	0.000	0.000	0.000	−0.167	0.185	0.333	0.333
RBDN-3	0.000	0.000	0.000	0.000	−0.056	0.098	0.000	0.000
RBDN-4	0.220	0.096	−0.414	0.195	0.500	0.167	0.000	0.365

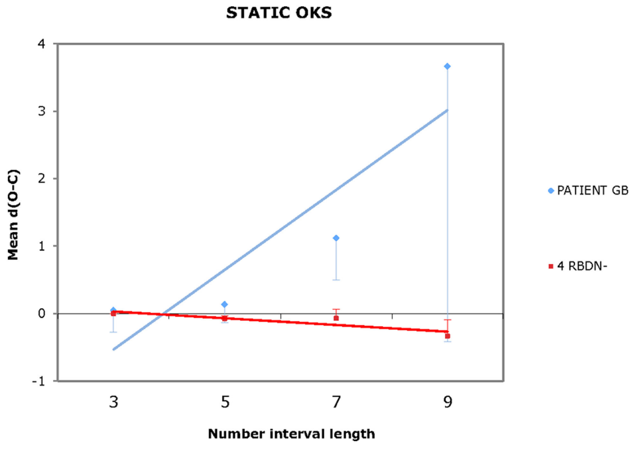

FIGURE 1 | In the static OKS condition, BG misbisected to the right of the true midpoint, as a function of number interval length.

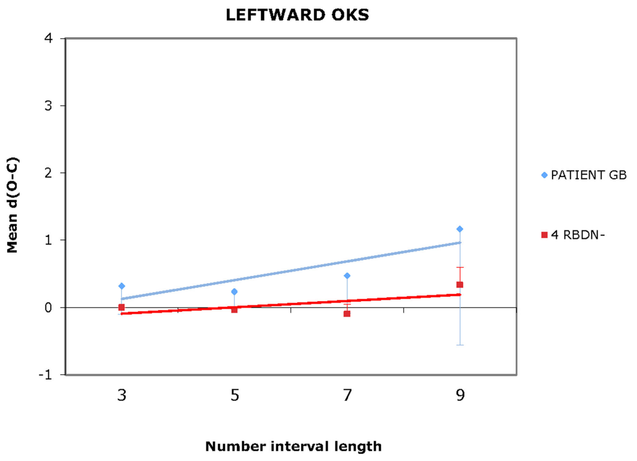

FIGURE 2 | In the leftward OKS condition, BG bisection did not differ from that of controls. Even for length 9 the mean dO–C of RBDN – did not differ from 0, $t(3) = 1.663$, $p = 0.194$.

OKS did not affect BG's performance in comparison to the static condition (compare **Figures 1** and **3**), we found that rightward OKS strongly decreased variability of response with respect to the static condition.

Neglect patients' response variability in visual line bisection is attributed to a pathologically extended "indifference zone" (Marshall and Halligan, 1989; Olk et al., 2004; Bonato et al., 2008). The "indifference zone" theory suggests that the bisection bias is due to an increased Weber fraction, which increases, in turn, the discrepancy between two lines, which are judged as equal in length. This accounts for the effect of line length (Marshall and Halligan, 1989) and for the inconsistent perception of the line center in neglect (Olk et al., 2004). Neglect severity is directly related to the size of the "indifference zone" (Bonato et al., 2008). The notion of "indifference zone" can be also applied to number interval bisection. In BG, both rightward and leftward OKS decreased variability with respect to the static condition. Thus, we suggest that the effect of biasing visuospatial attention in either direction through the OKS was to decrease the "indifference zone" and to make BG's responses more consistent than in the static condition. Note that variability in the rightward OKS condition was even smaller than that in the leftward OKS condition; this suggests that BG responded in the most consistent way when the attention bias induced by rightward

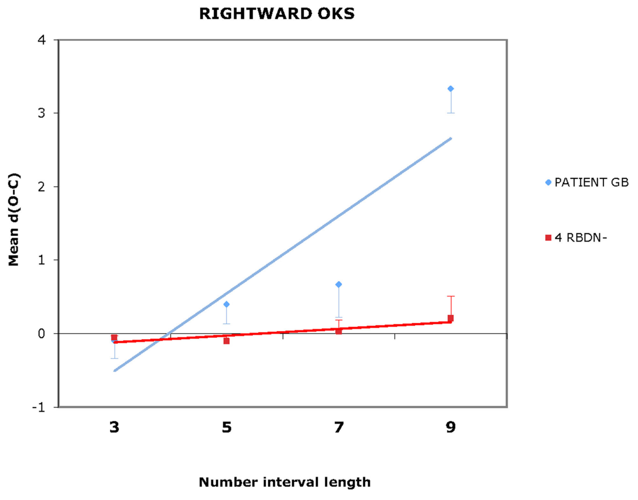

FIGURE 3 | In the rightward OKS condition, BG misbisected to the right of the true midpoint, as a function of number interval length. Even for length 9 the mean dO–C of RBDN – did not differ from 0, $t(3) = 1.414$, $p = 0.252$.

OKS had the same direction of the pathological attention bias (i.e., rightward) due to left neglect. The smaller variability in the rightward OKS condition also explains why the Pearson's r coefficient (correlation between dO–C and interval length) was larger in this condition compared to the static condition ($r = 0.41$ vs. $r = 0.25$), even though the mean dO–Cs were similar. Moreover, the fact that rightward OKS did not increase BG's bias in terms of dO–C over and above his dO–C in the static condition, is likely to reflect a ceiling effect.

Thus, OKS can influence not only the perceived space (for review, see Kerkhoff, 2003), but also the imaginal space of the MNL. Our findings run against the recent proposal that the misbisection pattern observed in neglect patients during mental number interval bisection is not due to neglect, but to a deficit in processing the initial items in a sequence to be held in verbal working memory (Fias et al., 2011; van Dijck et al., 2011). If this were the case, OKS should have not affected number interval bisection in BG, because the same verbal working memory resources were required in all the three OKS conditions (i.e., static, leftward, rightward) to perform the task. In contrast, the finding that the manipulation of visuospatial attention influenced BG's performance can be only explained by the hypothesis that his misbisection pattern was due to left neglect for the number space.

Our findings are in favor of a functional isomorphism (or homeomorphism) between the perceived space and the imaginal space of the MNL, as originally proposed by Zorzi et al. (2002). Indeed, the two spaces must have similar metrics (e.g., can be defined according to Cartesian coordinates) and can be modulated by the deployment of similar – though independent – spatial attention mechanisms. The independence of the number space from the perceived space is confirmed by double dissociations, which have been reported when left neglect patients bisect physical lines vs. mental number intervals (see Rossetti et al., 2004; Zorzi et al., 2004; Doricchi et al., 2005). Nonetheless, performance of left neglect patients in the two tasks is remarkably similar (Zorzi et al., 2006; Cappelletti et al., 2007) and can be correlated (Yang et al., 2009; see also Longo and Lourenco, 2007, for evidence of pseudoneglect). Furthermore, interactions between the perceived space and the imaginal space of the MNL have been revealed by the effects of spatial variables on number processing (for studies on left neglect patients, see Rossetti et al., 2004; Salillas et al., 2009; for studies on neurologically healthy participants, see Loetscher et al., 2008; Stoianov et al., 2008; Nicholls and McIlroy, 2010; Cattaneo et al., 2011; Kramer et al., 2011) and by the effects of numerical variables on spatial processing (for studies on left neglect patients, see Bonato et al., 2008; Loftus et al., 2008; for studies on neurologically healthy participants, see Fischer et al., 2003; Galfano et al., 2006; Casarotti et al., 2007; Cattaneo et al., 2009).

We conclude that our findings confirm and expand those of other studies revealing the presence of robust interactions between the deployment of attention in the perceived space and the deployment of attention in the imaginal space of the MNL. These interactions challenge both the verbal working memory account of number space in neglect patients (Fias et al., 2011; van Dijck et al., 2011) and the non-spatial accounts of number–space interactions that have been proposed by Gevers et al. (2006) and by Proctor and Cho (2006).

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The heterogeneous nature of number–space interactions

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It is generally accepted that the mental representation of numerical magnitude consists of a spatial "mental number line" (MNL) with smaller quantities on the left and larger quantities on the right. However, the amount of dissociations between tasks that were believed to tap onto this representational medium is accumulating, questioning the universality of this model. The aim of the present study was to unravel the functional relationship between the different tasks and effects that are typically used as evidence for the MNL. For this purpose, a group of right brain damaged patients (with and without neglect) and healthy controls were subjected to physical line bisection, number interval bisection, parity judgment, and magnitude comparison. Using principal component analysis, different orthogonal components were extracted. We discuss how this component structure captures the dissociations reported in the literature and how it can be considered as a first step toward a new unitary framework for understanding the relation between numbers and space.

Keywords: numbers, space, attention, working memory, SNARC, neuropsychology

INTRODUCTION

The representational nature of numbers has aroused the curiosity of many researchers. At present, one of the most influential and widely accepted model in numerical cognition is the triple code model of Dehaene (1992, Dehaene et al., 2003). This model postulates that, depending on the task, three independent representational systems are recruited: a visual system where numbers are encoded as strings of Arabic digits; a verbal system representing numbers lexically, phonologically, and syntactically; and a semantic quantity system which constitutes an abstract and non-verbal representation of numerical magnitude, the coding of which is thought to share functional properties and brain areas with the processing of space (e.g., Dehaene et al., 2003; Fias and Fischer, 2005; Hubbard et al., 2005; Umiltà et al., 2009).

One of the most convincing and robust observations that demonstrate the interaction between numbers and space is the spatial–numerical association of response codes (SNARC-) effect. When asked to judge whether a number is odd or even with a left or a right key press, people react faster to relatively large numbers (e.g., 9) with the right than with the left hand side, while the opposite is true for small numbers (e.g., 1). Dehaene et al. (1993) called this phenomenon the SNARC-effect and attributed it to the representation of number magnitude taking the shape of a horizontally oriented mental number line (MNL) with small numbers located on the left and large numbers on the right (at least in left-to-right reading cultures). Since then, this effect has been replicated in a wide variety of experimental settings and tasks, like for example parity judgment or magnitude comparison tasks.

Other convincing demonstrations of the tight relationship between number and spatial processing come from studies on neglect and pseudo-neglect (for a review see Umiltà et al., 2009). Patients with hemispatial neglect following right hemisphere lesion, suffer from deficient attentional orienting toward the contralesional left hemispace (for a review see Halligan et al., 2003). This deficit in spatial attention can be observed when these patients perform a physical line bisection task (e.g., Schenkenberg et al., 1980). Patients suffering from left sided neglect systematically shift their subjective midpoint of the line too far to the right (as if they neglect the left part of the line). Furthermore this bias progressively increases with longer lines, except for very short lines, where a paradoxical cross-over effect is typically found (Marshall and Halligan, 1989). Remarkably, patients suffering from neglect not only show a bias when bisecting physical lines, but also when they have to indicate the midpoint of a numerical interval (Zorzi et al., 2002). When asked for the number in the middle between two numbers (e.g., 1 and 9) they exhibited a bias toward a relatively large number (in this example, 7). Interestingly, the error pattern in this task is highly similar to that of the physical line bisection task, as also here, the misplacement of the midpoint was affected by the size of the number interval (i.e., a progressively larger bias toward larger numbers with increasing interval size, except for the shortest intervals where the crossover effect was observed).

Converging evidence for the functional link between spatial attention mechanisms and number processing comes from studies in other populations who are characterized by (subtle) attentional asymmetries. For example, in schizophrenic patients where a hemispheric imbalance is hampering the attentional orientating toward the right side of perceptual space (Michel et al., 2007), a bias toward smaller numbers in number interval bisection was observed (Cavezian et al., 2007). More recently, it has been shown that also in left brain damaged (right) neglect patients it is possible to observe a similar bias in number interval bisection (Pia et al., 2009). Finally, also healthy subjects show subtle biases in attentional processing toward the left side of space (i.e., pseudoneglect; for a review see Jewell and McCourt, 2000). Here again, a similar leftward bias is found during the bisection of both physical lines and number intervals (Longo and Lourenco, 2007).

The phenomenological similarity between the error pattern of the physical line and the number interval bisection task in both patients and healthy subjects is considered as evidence that the neurocognitive mechanisms of number–space interactions are the same as those that subserve spatial attention. Indeed, a currently widely accepted view states that all behavioral signatures of the relation between number and space (regardless of being measured in patients or healthy subjects) have their origin in a single spatially defined representation of number magnitude, conceivable as a MNL that is spatially defined in a way that is isomorphic (i.e., are organized along Cartesian coordinates) to the representation of perceptual space. That is, although the MNL is a representation in imaginal space and physical lines in perceptual space (which can doubly dissociate in neglect, see, e.g., Anderson, 1993; Guariglia et al., 1993), the two spaces are generated by highly similar and interactive spatial attention mechanisms (e.g., Zorzi et al., 2002; Fias and Fischer, 2005; Hubbard et al., 2005; Umiltà et al., 2009).

The close link between numbers and space and the involvement of a common mechanism of spatial attention is further supported by psychophysiological studies in healthy subjects using spatial attention paradigms (e.g., Fischer et al., 2003; Stoianov et al., 2008), in studies where attentional asymmetries were induced by means of TMS (e.g., Gobel et al., 2006; Rusconi et al., 2011), and in additional neuropsychological investigations in neglect. Regarding the latter, Vuilleumier et al. (2004) asked neglect patients to perform several magnitude comparison tasks and observed that they were slower to respond to the numbers adjacent to the left of the reference, i.e., their distance-effect[1] became asymmetrical, something which was not observed in right parietal patients without neglect and healthy controls. In addition, they also found that the magnitude comparison SNARC-effect selectively disappeared in the same neglect patients while it was clearly present in both control groups.

Although the MNL hypothesis provides a parsimonious account for the various empirical phenomena described above, evidence is beginning to accumulate that cannot be reconciled with the idea of a single underlying number representation that strongly depends on spatial-attentional resources. Where the MNL hypothesis predicts a strong relationship between neglect severity as measured with physical line bisection and the bias observed in several number–space tasks, recent studies indicate that physical line and number interval bisection can be doubly dissociated (e.g., Doricchi et al., 2005, 2009). At first sight this is reminiscent to the double dissociation reported between representational and perceptual neglect (e.g., Anderson, 1993; Guariglia et al., 1993). Indeed, number–space is usually considered as an instance of representational space (e.g., Vuilleumier et al., 2004), making it reasonable that it can be impaired independently from perceptual neglect (e.g., Umiltà et al., 2009). Recently however, a patient has been described who showed a clear within subject double dissociation between "right sided" perceptual and representational neglect on the one hand, and "left sided" neglect in number–space on the other (van Dijck et al., 2011). This observation suggests that the attentional difficulties associated with neglect (irrespective of being observed in representational or perceptual space) are neither a necessary nor a sufficient condition to evoke a bias when bisecting number intervals. Moreover, these observations also suggest that different cognitive processes underlie the interval bisection and the line bisection task. In line with this, Doricchi et al. (2009) observed a correlation between difficulties in the retention of verbal and spatial sequences in working memory and the number interval bisection task. Additionally, these functional results were complemented by anatomical findings demonstrating that the patients showing a rightward number interval bisection bias had a maximal lesion overlap in the prefrontal area's that are associated with short-term working memory, whereas those showing a rightward bisection bias both in physical and number–space had supplementary lesion involvement of the temporal–parietal junction, an area that can be relevant for attentional neglect (Vallar and Perani, 1986; Corbetta and Shulman, 2002) but not for number processing.

The idea that the behavioral signatures of the interaction between numbers and space are not unequivocally attributable to a shared underlying mechanism was corroborated by other recent observations. For example, Priftis et al. (2006) described neglect patients who exhibited a number interval bisection bias while presenting a normal SNARC-effect in a parity judgment task. This suggests that number bisection and the SNARC-effect rely on (at least partially) distinct mechanisms. This is in line with recent studies in neurologically healthy subjects (Gevers et al., 2010) that cast doubt on the visuo-spatial nature of the SNARC-effect by demonstrating that the effect is the result of verbal–spatial coding of space (i.e., the association of the concepts small/large and left/right, see Proctor and Cho, 2006 for a theoretical elaboration on this principle), rather than of a spatial coding in the form of a MNL. Extending upon those findings, van Dijck et al. (2009) observed that the SNARC-effect selectively disappeared in parity judgment while (healthy) subjects were keeping verbal information in memory, and in magnitude comparison while keeping visuo-spatial information in memory (see also Herrera et al., 2008). They concluded that numbers can be associated with different spatial codes in different tasks and that those associations draw upon working memory resources (see also van Dijck and Fias, 2011), thereby supporting the idea that the representational nature of numbers is more complex than originally proposed by the MNL hypothesis.

Altogether, these recent findings suggest that the relation between numbers and space cannot be attributed to one single underlying mechanism (see Chen and Verguts, 2010 for an elegant computational model incorporating this idea). In the present study, we tried to shed more light on the diversity of the number–space interactions and their underlying cognitive mechanisms by directly comparing the different tasks and populations that are typically used to illustrate these interactions. For this purpose, we subjected a group of right brain damaged patients and age and education matched healthy participants to a battery of tasks comprising physical line bisection, number interval bisection,

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[1] The distance-effect in magnitude comparison is the observation that reaction times linearly increase in function of the distance of the to-be-compared number to the used reference number (see, e.g., Moyer and Landauer, 1967).

parity judgment, and magnitude comparison. Using principal component analysis (PCA), we unraveled the internal structure of the "number–space" by identifying groups of variables that are interrelated via latent factors. Based on the idea of a common MNL underlying the SNARC-effect and number interval bisection, which shares functional properties with the processing of perceptual lines, all measured variables should highly load on the same principal component. On the other hand, the different dissociations observed within the domain suggest a more complex interrelation from which it is predicted that the different tasks will load on different components. Although the exact pattern of relations is yet unclear, the differential contribution of verbal and spatial working memory resources to the parity judgment and magnitude comparison SNARC-effect (van Dijck et al., 2009), suggests that both tasks tap on different components. Similarly the observed dissociation between physical line and number interval bisection in neglect patients, suggests that the bias observed in both tasks can also be associated with different components. For the sake of comparability with previous studies, we also applied traditional ANOVA group analyses to verify whether all classically reported group effects could be replicated. Moreover, in addition to the group ANOVAs and PCA, we evaluated whether or not our data contained dissociations at the level of the individual subjects.

MATERIALS AND METHODS

PARTICIPANTS

Seventeen patients with right brain damage were recruited based on the presence or absence of clinical neglect symptoms from the rehabilitation unit of Hof ter Schelde (Antwerp) and from the Neurological department of Erasmus University Hospital Brussels. Initial selection of patients was based on clinical manifestations reported in the medical file and the results of formal general neuropsychological evaluation. Since for some patients there was a gap of several weeks to months between the initial selection and participation in the current study, final assignment to the neglect or non-neglect group was based on the results of the physical line bisection at the time of the current study. For this purpose the data of the age and education matched healthy controls (see below) were used to calculate the 3 SD cut-off value which was used to determine abnormal asymmetries in spatial attention. For all except one patient (subject 2 of the control group), this procedure confirmed the clinical observations. For this patient, the clinical descriptions of neglect were not consistent. Given his normal performance in the current physical line bisection task, his normal performance in the other task and the time lag of more than 3 months between the final neuropsychological evaluation and the moment of participation, it was decided to include him in the control group (importantly, the results of the PCA reported below were virtually identical when this subject was excluded from the analyses or considered as a neglect patient). By means of this procedure, 10 patients were considered as neglect patients (nine males; average age: 65.50 years; SD = 13.03; average education: 10.6 years; SD = 4.79) and 7 as patients without neglect (four males; average age: 63.26 years: SD = 10.80; average education: 13.71 years; SD = 5.19) All brain damaged patients suffered from a recent right hemispheric stroke and suffered from left sided hemiplegia or hemiparesis. In the control group, 12 aged and education level matched healthy controls (four males; average age: 69 years; SD = 12; average education: 13.17 years; SD = 4.53) were included. The study was approved by the local ethical committee of the faculty of Psychology and Educational sciences of Ghent University. According to the Declaration of Helsinki, an informed consent was signed before participation. Demographic, clinical, and psychometric data of the patients are reported in **Table 1**.

DESIGN

In a session of approximately 1 h, all subjects participated in line bisection, number interval bisection, magnitude comparison and parity judgment. Tasks were presented in counterbalanced order with the restriction that the sessions started and ended with either the comparison or parity judgment task. Both the magnitude comparison and parity judgment task consisted of two blocks that differed in response mapping (i.e., assignment of magnitude (or parity) status to left or right response). These blocks were successively administered with a part of the line bisection task (consisting of three parts) administered in between. After the first SNARC-task was completed, the number interval bisection and the second part of the line bisection task were administered.

Both the order and response mapping of both SNARC-tasks were counterbalanced. In the patient group, eight started with the magnitude comparison task, of which four started with the compatible mapping (i.e., odd/smaller → left button, even/larger → right button). The other nine subjects began with parity judgment, of which five started with the compatible mapping. For the healthy controls both task order and response mapping were equally balanced across subjects.

STIMULI AND MATERIAL

Line bisection

Fifteen horizontal lines of three different lengths (2, 10, and 20 cm; line thickness 2.5 mm) were presented one by one, each centered on a separate landscape A4 paper. The instructions were to mark the midpoint of these lines with a pencil. Lines of the same length were presented in separate blocks that were presented at different moments in the experimental session (see Design). The order of presentation of the different blocks was randomized across participants. All lines were aligned to the body midline. Head and eye movements were allowed, but moving the test sheet was not permitted. No time constraints were imposed.

Interval bisection

Forty-eight numerical intervals were orally presented and subjects were asked to verbally indicate the numerical midpoint with the explicit instruction not to calculate. The number pairs were constructed following the method described in Zorzi et al. (2002). All number intervals were presented randomly (e.g., which number is in the middle of 1 and 9?). For each interval, the smallest number was presented first. No time constraints were imposed and the intervals were repeated if requested. It was not explicitly encouraged to use spatial imagery.

Parity judgment and magnitude comparison

For both tasks, digits ranging from 1 to 9 (with the exception of 5) had to be judged on the basis of parity (odd or even) or magnitude

Table 1 | Demographic, clinical, and psychometric data of the patient sample.

Subject	Group	Sex	Age (years)	Education (years)[1]	Handedness	Type lesion	Location[2]	Months after onset	Left plegia/ paresis[3]	Parity judgment[4]	Number comparison	Computing average[5]
1	Neglect patients	M	73	6	Right	Ischemic	F–T–P	2, 5	+	92	92	48
2		M	64	12	Right	Ischemic	MCA	1, 5	+	76	94	47
3		M	80	16	Right	Ischemic	MCA	3, 5	+	91	95	46
4		M	77	8	Right	Ischemic	Basal ganglia	5, 5	+	85	95	48
5		M	75	6	Right	Ischemic	F–P–internal capsule	2	+	86	96	46
6		F	53	12	Right	Hemorrhage	F–T–P (incl. ventricles)	27, 5	+/–	94	94	NA
7		M	67	6	Right	Ischemic	Subcortical	9	+	84	90	NA
8		M	63	6	Right	Ischemic	MCA–putamen	2	+	95	93	NA
9		M	67	17	Right	Ischemic	T–P–lenticular capsule	2	+	96	96	45
10		M	36	17	Right	Ischemic	Sylvian artery	1	+	96	96	24
1	Patients without neglect	M	72	15	Right	Ischemic	P	1	+/–	93	93	45
2		M	64	24	Right	Hemorrhage	F–T–P	1	+	94	95	47
3		F	64	12	Right	Ischemic	MCA, corona radiata	9	+	93	96	41
4		F	59	8	Right	Ischemic	Pontine	1	+/–	96	95	39
5		M	75	12	Right	Ischemic	NA	2	+	93	94	48
6		F	42	15	Right	Ischemic	T–P	2	+/–	95	95	NA
7		M	67	10	Right	Ischemic	NA	1	+/–	91	94	48
1	Healthy controls	M	69	12	Left					95	95	46
2		F	66	6	Right					95	96	44
3		F	52	20	Right					95	96	44
4		F	81	8	Right					96	94	42
5		M	78	12	Right					81	96	47
6		F	76	11	Right					94	96	44
7		F	72	12	Right					96	96	45
8		M	71	12	Right					96	96	48
9		F	51	12	Right					95	94	48
10		F	80	22	Right					94	96	44
11		M	66	15	Right					95	95	46
12		F	61	16	Right					96	96	46

[1]The years of education reflect the amount of years of full time schooling; [2]F, frontal; T, temporal, P, parietal; MCA, middle cerebral artery; NA, not available; [3] "+" refers to the presence of hemiplegia and "+/–" to hemiparesis; [4]The data of the parity judgment and magnitude comparison task reflect the performance of the compatible response mapping (for full description see below; max score: 96). [5]As trials for which the average needed to be calculated, the number pairs of the interval bisection task were used (max score: 48); NA, not available.

(smaller or larger than 5). Both tasks consisted of two blocks differing in response mapping (odd-left and even-right or vice versa; small-left and large-right or vice versa). Each digit was presented 12 times for each response mapping condition. This resulted in a total of 192 trials per task.

For both tasks, a trial started with the presentation of a fixation point (#) for 700 ms. Thereafter the target number was presented until a response was given. Only reaction times below 10000 ms were considered as actual responses. The digits were presented in a random order in the center of the computer screen. Sitting distance from the screen was approximately 60 cm. Stimuli (1 by 1.4 visual degrees) were presented in white against a black background. Before running the experiment, it was verified whether the subjects could easily pay attention to the digits on the screen. To get used to the experimental procedure, each response mapping block of both tasks was preceded by eight exercise trials in which each digit was presented once. Twenty-eight subjects used a PC mouse as response interface and were asked to press the left button with their right index finger and the right button with the right middle finger (cf. Priftis et al., 2006). Due to difficulties in subtle movements, one neglect patient was asked to respond with a joystick by making left and rightward movements.

RESULTS

ANALYSES OF GROUP DIFFERENCES

Bisection tasks

To evaluate the presence of (pseudo) neglect in physical line and number interval bisection, the response bias was evaluated by measuring the distance of the subjective midpoint from the actual midpoint. For the line bisection task, distances were measured with a ruler from the left side of the line with 0.5 mm accuracy and for the interval bisection bias from the smallest number. For each trial, these values were transformed to a deviation score by means of the following formula (Schenkenberg et al., 1980):

$$\text{deviation score} = \frac{\text{measured left half} - \text{true half}}{\text{true half}} \times 100$$

With this formula, a positive score is obtained when the subjective midpoint is shifted rightward when bisecting a line or when an overestimation is made in the number interval bisection task. For each subject separately, the deviation scores of all trials were entered into a *regression analysis* for repeated measures designs (Method 3 of Lorch and Myers, 1990) with line or interval length as predictor. The sign of the regression weights, obtained with this method, indicates the direction in which the midpoint is misplaced. The size of those weights reflects the degree in which this bias is modulated by line or interval length. In this way, a positive regression weight indicates that the midpoint is progressively overestimated/shifted more to the right of the true midpoint and is, when large enough, interpreted as a manifestation of neglect. A negative regression weight, on the contrary, indicates pseudo-neglect. The intercept is considered as an index of the cross-over effect. A negative intercept indicates a cross-over toward the left/smaller numbers.

To evaluate whether the average weights and intercepts significantly differ from zero, *one-sample t-tests* were performed for each subject group separately. Finally, *one-way ANOVA's* were performed with the regression weights and the intercepts as dependent and group membership as independent variable, to verify the presence of group differences. In case the factor group membership turned out to be significant, *Bonferroni corrected post hoc* analyses were performed to get more insight in the nature of the effect.

Based on the existing literature (e.g., Zorzi et al., 2002), a positive regression weight and a negative intercept is to be expected in neglect patients, whereas in healthy controls a negative regression weight and a positive intercept should be found, indicating the presence of neglect and pseudo-neglect respectively (Longo and Lourenco, 2007).

Physical line bisection. The neglect group bisected 11% (SD = 8%) of the lines correctly, the patients without neglect 23% (SD = 13%), and the healthy controls 26% (SD = 13%). An overview of the average deviation scores for each line length of each subject group is provided in **Figure 1A**. The average regression weight of the neglect group was +1.00% (SD = 0.31%), [$t(9) = 10.31$, $p < 0.001$ (one-sided)] of the patient without neglect +0.02% (SD = 0.26%), [$t(6) = 0.23$, $p > 0.99$ (one-sided)] and of the healthy controls −0.20% (SD = 0.23%), [$t(11) = -2.90$, $p < 0.01$ (one-sided)]. A *one-way ANOVA* with these regression weights as dependent variable and subject group as factor indicated group differences in the magnitude of these weights [$F(2,26) = 59.07$, $p < 0.001$]. *Post hoc* comparisons revealed that the regressions weights of the neglect group differed from the patients without neglect and the healthy controls (both p's < 0.01) but that no differences were observed between the two control groups. This pattern of results confirmed the presence of left sided neglect in the neglect group, and the presence of right sided pseudo-neglect in the healthy controls.

To evaluate the presence of a cross-over effect, similar analyses were performed on the intercepts of the three subject groups. The presence of a (left sided) cross-over effect was confirmed in the neglect group as the average intercept was −9.83% (SD = 4.57%), [$t(9) = -6.81$, $p < 0.001$ (one-sided)]. Where the effect did not reach significance in the patient without neglect [average intercept: −1.09%; SD = 6.53%; $t(6) = -0.44$, $p > 0.99$(one-sided)], the healthy controls showed a (right sided) cross-over effect [average intercept: 1.86%; SD = 3.56%; $t(11) = 1.81$, $p < 0.05$ (one-sided)]. The *one-way ANOVA* showed again group differences [$F(2,26) = 17.28$, $p < 0.001$]. As for the regression weights, *post hoc* comparisons revealed that only for the neglect group the differences with the other groups were *significant* [both p's < 0.001].

Number interval bisection. The neglect group bisected 70% (SD = 18%) of the intervals correctly, the patients without neglect 80% (SD = 12%), and the healthy controls 88% (SD = 5%). An overview of the average deviation scores for each interval size of each subject group is provided in **Figure 1B**. Like in the line bisection task, the presence of a significant bias was evaluated by means of the regression approach. The average regression weight of the neglect group was +6.16% (SD = 6.22%), [$t(9) = 3.13$, $p < 0.01$ (one-sided)] of the patient without neglect +0.58% (SD = 4.25%), [$t(6) = 0.36$, $p > 0.99$ (one-sided)] and

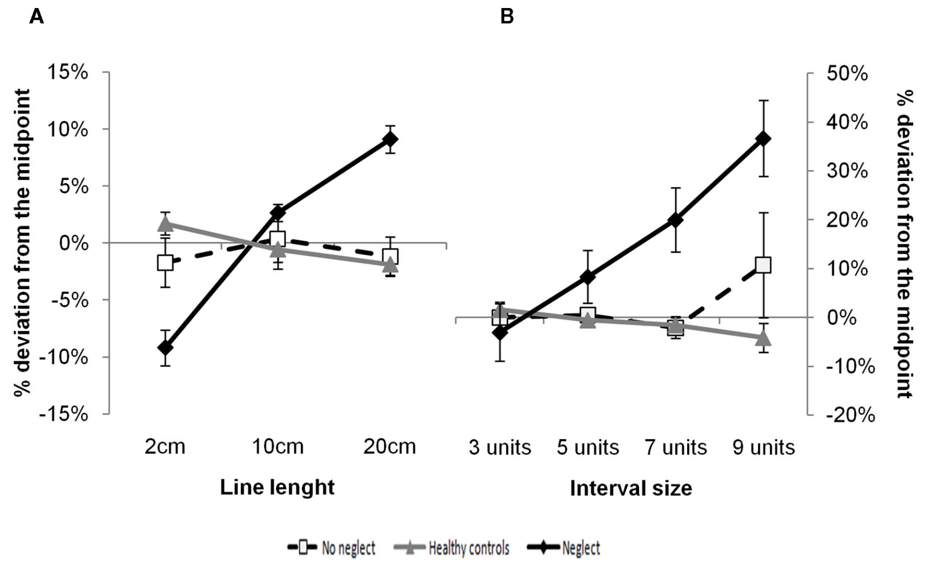

FIGURE 1 | Physical line bisection (A) and number interval bisection (B) in neglect patients, patients without neglect and healthy controls. Both figures show the average proportional difference between reported and correct midpoints for the different line and interval lengths. Zero reflects a correct response, while positive values indicate a rightward shift or an overestimation of the midpoint and negative values a leftward shift or an underestimation. Error bars give the SEM across subjects.

of the healthy controls −0.88% (SD = 1.16%), [$t(11) = -2.63$, $p = 0.01$ (one-sided)]. A *one-way ANOVA* with these regression weights as dependent variable and subject group as factor indicated group differences in the magnitude of these weights [$F(2,26) = 7.87$, $p < 0.01$]. *Post hoc* comparisons revealed that the regressions weights of the neglect group differed from the patients without neglect and the healthy controls [both p's < 0.05] but that no differences were observed between the two control groups.

The data were further inspected for the presence of a cross-over effect. For this purpose, the analyses reported above were repeated with the individual intercepts obtained from the regression analyses as dependent variable. The presence of a (left sided) cross-over effect was confirmed in the neglect group with an average intercept of −21.92% (SD = 32.90%), [$t(9) = -2.16$, $p < 0.05$ (one-sided)]. The effect did not reach significance in the patients without neglect [average intercept: −2.33%; SD = 23.40%; $t(6) = -0.26$, $p > 0.99$ (one-sided)], the healthy controls showed a (right sided) cross-over effect [average intercept: 4.14%; SD = 7.79%; $t(11) = 1.84$, $p < 0.05$ (one-sided)]. The *one-way ANOVA* showed again group differences [$F(2,26) = 3.79$, $p < 0.05$]. *Post hoc* comparisons revealed that only the neglect group differed significantly from the healthy controls [$p < 0.05$]. Altogether, this pattern of results replicates previous reports on number interval bisection (e.g., Zorzi et al., 2002; Priftis et al., 2006; Longo and Lourenco, 2007), and confirms the phenomenological similarity between neglect observed in physical line and number interval bisection both in neglect patients as in healthy controls.

Parity judgment and magnitude comparison SNARC-effect

For both tasks, only correct responses and RT's larger than 150 ms and smaller than the individual 2.5 SD from the average RT cut-off were included in the analyses. For both the parity judgment and magnitude comparison task, the SNARC-effect was determined using the regression approach described in Fias et al. (1996). For this purpose, dRT's (average RT right response – average RT left response) were computed for each number separately. Per subject, these dRT's were entered in a regression analysis with magnitude as predictor. The regression weight of the magnitude predictor expresses the size of the SNARC-effect. A *one-sample t*-test was then used to evaluate whether the averages of the individual regression weights of each subject group significantly differed from zero. To verify the presence of group differences, similar *one-way ANOVA's* were carried as in the bisection tasks.

Based on the existing literature, in parity judgment, comparable negative regression weights are expected in all subject groups (Priftis et al., 2006), while in magnitude comparison, negative regression weights are only expected in both control groups (Vuilleumier et al., 2004).

Parity judgment SNARC-effect. Given the inclusion criteria, for the neglect group, the control patients and the healthy controls, 88.59% (SD = 6.66%), 94.87% (SD = 2.39%), and 94.27% (SD = 4.77%) of the trials were included in the analyses, respectively. The overall average RT for those subject groups was 1092 ms (SD = 281 ms), 735 ms (SD = 173 ms), and 671 ms (SD = 107 ms) respectively. A preliminary analysis showed no influence of the different counterbalancing factors (order of presentation of SNARC-tasks, order of response mapping or their interaction) for the group effects described below, and confirmed the absence of a speed–accuracy trade of in any of the subject groups (for all positive correlations p-values were larger than 0.49).

For all subject groups a negative relation between the predictor variable (number) and the criterion variable (dRT) was observed (see **Figure 2A**). The average regression weight of the neglect

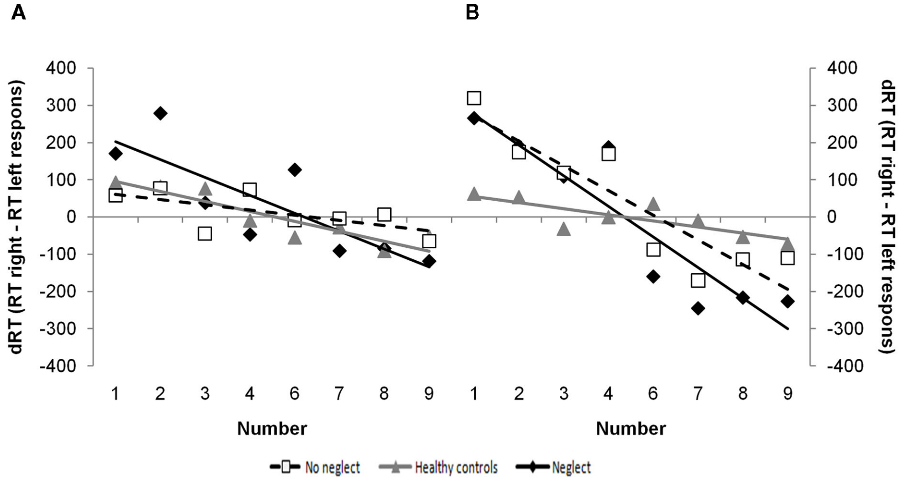

FIGURE 2 | SNARC-effects of magnitude comparison and parity judgment in neglect patients, patients without neglect and healthy controls. The observed data and the regression line represent the response time differences (dRT) between right and left responses as a function of the numerical magnitude in parity judgment **(A)** and magnitude comparison **(B)**.

group was −38.79 (SD = 47.69), of the control patients −11.76 (SD = 8.06) and of the healthy controls −22.59 (SD = 15.93). The obtained weights were compared against zero with a *one-sample t-test*. This test showed that for all subject groups the regression weights were significantly different from zero [all t's(9,6,12) < -2.57, all p's < 0.016 (one-sided)]. In line with the predictions, the size of the SNARC-effect was comparable in all subject groups as the *one-way ANOVA* with those regression weights as dependent and group membership as independent variable failed to reach significance [$F(2,26) = 1.75$, $p = 0.19$].

Magnitude comparison SNARC-effect. Given the inclusion criteria, for the neglect group, the control patients and the healthy controls, 87.86% (SD = 6.81%), 92.49% (SD = 4.07%), and 97.09% (SD = 1.36%) of the trials were included in the analyses, respectively. The overall RT for those subject groups was 1069 ms (SD = 156 ms), 768 ms (SD = 189 ms), and 627 ms (SD = 119 ms). A preliminary analysis showed no influence of the different counterbalancing factors (order of presentation of SNARC-tasks, order of response mapping or their interaction) for the group effects described below, and confirmed the absence of a speed—accuracy trade of in any of the subject groups (for all positive correlations p-values were larger than 0.38).

In magnitude comparison too, all subject groups demonstrated a negative relation between the predictor variable (number) and the criterion variable (dRT; see **Figure 2B**). The average regression weight of the neglect group was −70.87 (SD = 73.22), of the control patients −56.99 (SD = 39.02) and of the healthy controls −12.97 (SD = 23.61). The obtained weights were compared against zero with a *one-sample t-test*. This test showed that for all subject groups the regression weights were significantly different from zero [all t's(8,6,12) < -1.90, all p's < 0.05 (one-sided)]. The *one-way ANOVA* with those regression weights as dependent and group membership as independent variable was significant [$F(2,25) = 4.12$, $p = 0.028$], indicating group differences in the size of the SNARC-effect. *Post hoc* analyses demonstrate that the SNARC-effect of the neglect group is larger compared to the healthy controls' [$p < 0.05$] but that the effect of the control patients did not differ from the two other groups [both p's > 0.19].

Asymmetry of the magnitude comparison distance-effect

Similar inclusion criteria were used as for the calculation of the SNARC-effect, leading to the same descriptive statistics. Preliminary analyses again showed no influence of the different counterbalancing factors (order of presentation of SNARC-tasks, order of response mapping and their interaction) on the effects found in the *repeated measures* ANOVA described below.

To investigate the presence of a potential asymmetry in the distance-effect, average RT's were computed for each number separately, and submitted to *repeated measures ANOVA* with magnitude (two levels: smaller and larger than 5) and distance from the referent (four levels) as within subject and group membership as between subject variables. This analysis revealed a main effect of group membership [$F(2,26) = 23.80$, $p < 0.01$] and of distance [$F(3,78) = 10.53$, $p < 0.01$]. Slower responses were given by the neglect patients (1069 ms) than by the patients without neglect (769 ms) and the healthy controls (628 ms). Average RTs per distance, from distance 4 to distance 1, were 801, 803, 812, and 872 ms, respectively. A polynomial contrast confirmed a linear trend [$F(1,26) = 25.95$, $p < 0.001$], indicating the presence of a distance-effect. In addition, an interaction between magnitude and distance [$F(3,78) = 3.97$, $p < 0.05$], and a triple interaction [$F(6,78) = 3.73$, $p < 0.01$] between magnitude, distance, and group membership was observed (see **Figure 3**).

To get more insight in the nature of the triple interaction, the RT's for the small and large numbers of each individual subject were entered into separate *regression analyses* with their distance toward the referent (number 5) as predictor. To obtain an index of the asymmetry, the obtained regression weights of large numbers were subtracted from the weights obtained for the small numbers.

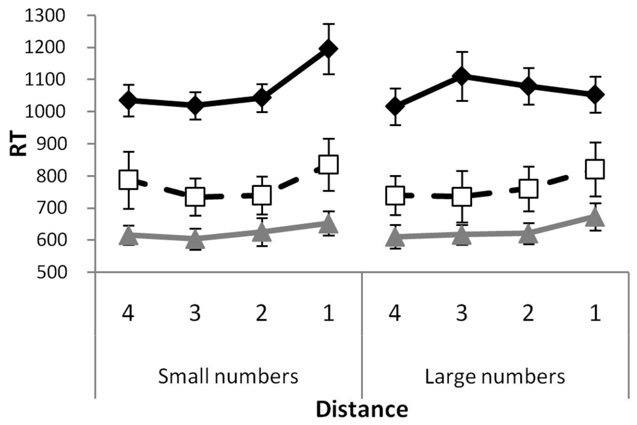

FIGURE 3 | Distance effects for small and large numbers separately in neglect patients, patients without neglect and healthy controls. The data points reflect mean reaction times and the error bars give the SEM across subjects.

In this context, a negative asymmetry index reflects a stronger distance-effect for small numbers. Given the existing literature (Vuilleumier et al., 2004), a negative index is to be expected for neglect patients.

The average asymmetry index of the neglect group was −42.82 ms (SD = 38.80), of the control patients 12.27 (SD = 33.53), and of the healthy controls 5.89 (SD = 18.86). The obtained weights were compared against zero with a *one-sample t-test.* This test showed that only for the neglect group the asymmetry index were significantly different from zero [$t(9) = -3.49$, $p < 0.01$ (one-sided)]. The *one-way ANOVA* with those indexes as dependent and group membership as independent variable was significant [$F(2,26) = 9.27$, $p < 0.01$], indicating group differences. *Bonferroni corrected post hoc* analyses demonstrate that the asymmetry index of the neglect is significantly different from both control groups [both p's < 0.01] and that no difference was observed between the healthy controls and the patients without neglect [$p = 1.00$].

THE SEARCH FOR (DOUBLE) DISSOCIATIONS AT THE INDIVIDUAL LEVEL

Although the group analyses described above demonstrate a phenomenological similarity between the performance on physical line and number interval bisection in neglect patients and healthy control subjects, one should be careful to draw conclusions, because averaging across individuals may obscure the possible presence of (double) dissociations within individuals. Therefore, we also performed a multiple case analysis. We first calculated the average effect sizes for all tasks in the healthy control group. Then, for each patient, we used + and – 3 SD of this control group average effect size as a boundary to define whether the patients performance was inside or outside the normal range. An overview of this analysis can be found in **Figure 4**. A visual inspection of this figure reveals that, like observed by Doricchi et al. (2005, 2009), a meaningful number of neglect patients (4 out of 10) showed a normal performance in number interval bisection, whereas 2 out of 7 patients without neglect, showed an abnormal rightward bias in number interval bisection. Interestingly, the same double dissociation was observed for the asymmetry of the distance-effect. Here 4 out of 10 neglect patients did not show an abnormal asymmetry, while 1 control patients without neglect showed an opposite asymmetry. These results clearly demonstrate that neglect in perceptual space is not sufficient to give rise to neglect in the number domain, and that a biased number processing is not in all cases an indication for the presence of neglect.

PRINCIPAL COMPONENT ANALYSIS

Based on the results reported so far, it is clear that conclusions based on the analyses of group differences and on the multiple case approach diverge. Drawing conclusion about the nature of the relationship between variables based on binned data (or based on clinical observations, or on the use of cut-offs), however, has the potential risk of misinterpreting the actual relationship between the involved variables. As an alternative, correlational methods have been proposed (e.g., MacCallum et al., 2002). For this purpose, we further analyzed the available data by means of a PCA to get a clearer picture of the interrelation of the effects measured in the study. To prevent that the PCA would capture the subject group differences instead of the interrelation between the different tasks, the data of all variables were normalized to z-scores for each subject group separately in advance. The current PCA was conducted on the correlation matrix of the normalized regression weights of the interval bisection, physical line bisection, parity judgment SNARC-effect, magnitude comparison SNARC-effect, and the asymmetry index of the distance-effect. This data matrix contained one missing value (magnitude comparison SNARC-effect for neglect patient no 7) which was substituted by the neglect group's average. No constraints in the amount of extracted factors were imposed. An overview of these individual data is presented in **Figure 4**. For the ease of interpretation, the directionality of the dependent variables was adjusted so that a larger positive number always indicates a larger effect.

Because PCA is a multivariate technique that assumes multivariate normal distributions, it is very sensitive to extreme uni- and multivariate outlier. Therefore, scrutinous evaluation of the normality assumption is needed (Raykov and Marcoulides, 2008). A careful verification revealed no uni- or multivariate outliers, as all values were within the ±3 SD from the average range and for all subjects the Mahalanobis distance was smaller than the 0.05 critical value. Furthermore, satisfactory uni- and multivariate distributions were obtained for all variables [Omnibus test of normality (Jarque and Bera, 1987): all LM's < 3.50; all p's > 0.17; Omnibus test of Multivariate normality (Looney, 1995) VQ$^3(10) = 12.63$, $p > 0.24$].

Results

The Bartlett's test of sphericity turned out to be significant ($\chi^2 = 19.18, p < 0.05$) indicating that the data matrix is suitable for PCA (Raykov and Marcoulides, 2008). According to Kaiser's criterion, a three component solution (all eigenvalues >1.02), explaining 78% of the variance, was chosen. The initial solution was (raw) varimax rotated to obtain a simple structure (see **Table 2**). To evaluate the relevance of the obtained factor loadings, only statistically significant factor loadings (p-values obtained by correlating the

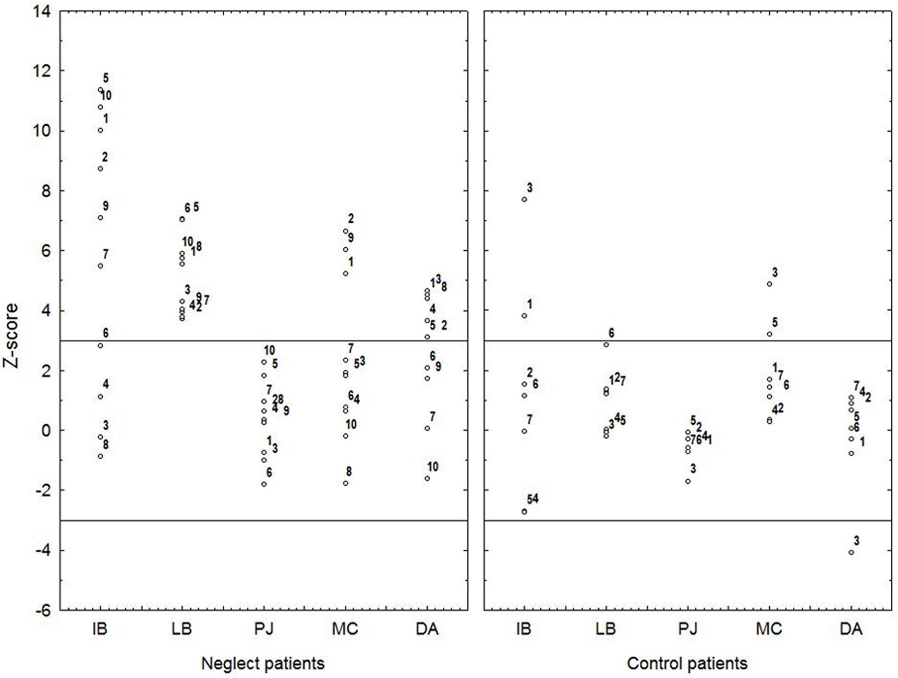

FIGURE 4 | Overview of the individual data points for both patient groups separately of the different tasks that were used for the PCA. Each data-point reflects the *z*-score values based on the average and SD of the healthy controls, and the directionality of the dependent variables was adjusted so that a larger positive number always indicates a larger effect. The black lines indicate the ±3 SD from the average interval calculated on the data of the healthy controls. Each point reflects a data point of one subject for a specific task. Subject numbers were kept constant over the different tasks and correspond to the subject numbers reported in **Table 1**. IB, interval bisection; LB, line bisection; PJ, parity judgment; MC, magnitude comparison; DA, distance asymmetry.

dependent variables with the obtained individual factor scores on the three components) are reported. In this way, the first component had substantial loading from the number interval bisection [$r = -0.80$, $p < 0.001$] and the magnitude comparison SNARC-effect [$r = -0.80$, $p < 0.001$]. The second component was highly loaded by the line bisection task [$r = 0.95$, $p < 0.001$] and on the asymmetry index of the distance-effect [$r = 0.39$, $p < 0.05$] and the third component highly loaded on the parity judgment SNARC-effect [$r = -0.71$, $p < 0.001$], the asymmetry index of the distance-effect [$r = 0.78$, $p < 0.001$], and the interval bisection task [$r = -0.40$, $p < 0.05$]. Thus in contrast with the idea that only one cognitive mechanism determines the variability in number–space interactions, a clear three component solution was observed (note that a three component solution was also found when the PCA was conducted on the raw data, where no normalization procedure was applied to level out grouping effects). A discussion of how the obtained internal structure capture with the dissociations described in the literature is provided in the Section "General Discussion."

Table 2 | Overview of the three component solution obtained from the PCA.

Loading on factor	Component1	Component2	Component3
Number interval bisection	−0.80		−0.40
Line bisection		0.95	
PJ SNARC			−0.71
MC SNARC	−0.80		
Distance asymmetry		0.39	0.78
Eigenvalue	1.40	1.18	1.31
Percentage explained variance	28	24	26

Only significant loadings are listed.

GENERAL DISCUSSION

The aim of the present study was to uncover the relations between different effects that are assumed to reflect the interactions between numbers and space. For this purpose a group of right brain damaged patients with neglect, a group of right brain damaged patients without neglect and healthy controls participated in physical line bisection, number interval bisection, parity judgment, and magnitude comparison. First, using traditional group analyses we showed that the basic effects were obtained as expected. Subsequently, we went beyond the group level analysis and looked at the pattern of dissociations between the tasks at the level of the individual patients. Finally, the data from all tasks and subjects were entered into a PCA to reveal their internal structure.

Concerning the group analyses, as expected from the literature (Zorzi et al., 2002; Priftis et al., 2006), a phenomenological similarity in the error patterns of the physical line and number interval bisection task was found in left neglect patients, who showed a right systematic bias which increased as a function of the line/interval length, and a cross-over effect for the short lines/intervals. In addition, the error pattern (both in terms of the cross-over effect as the bias which is modulated by line length) was also similar in both tasks for the healthy controls, where right sided pseudo-neglect was observed. Furthermore, as observed by Vuilleumier et al. (2004), the influence of neglect was also manifest in the number comparison distance-effect of the neglect patients, which was more asymmetrical due to a stronger distance-effect for small numbers (that are on the left of the referent). In addition, replicating the observations described by Priftis et al. (2006), the parity judgment SNARC-effect was comparable for all subject groups. In contrast to the observations of Vuilleumier et al. (2004) however, a significant magnitude comparison SNARC-effect in neglect patients was found, which was comparable to the effect of the patients without neglect.

Further evaluation whether or not the data of the individual subjects fell within the normal range revealed that, despite the phenomenological similarities at the group level, not all neglect patients struggled with a bias in number interval bisection and with an asymmetric distance-effect, and that some of the patients without neglect showed a significant bias in interval bisection. These findings clearly demonstrate that perceptual neglect and neglect in number–space can be doubly dissociated.

Finally and most importantly, the PCA resulted in a three component structure that accounted for 78% of the variance. The first component had substantial loading from interval bisection and the magnitude comparison SNARC-effect. The second component was associated with physical line bisection and the asymmetry of the distance-effect, and the third component included interval bisection, parity judgment SNARC-effect, and the asymmetry of the distance-effect.

So far, it was a widely accepted idea that all behavioral signatures of the number–space interactions have their origin in a single spatially defined representation of number magnitude, conceivable as a MNL, which shared functional properties with the way how (perceptual) space is represented and processed (e.g., Zorzi et al., 2002; Hubbard et al., 2005; Priftis et al., 2006). A straightforward prediction of this account is that only one component should be extracted when PCA is used to get an idea about the latent components underlying the various behavioral effects. This is because the MNL hypothesis assumes strong mutual relationships between its behavioral signatures themselves and between those signatures and measures of attentional asymmetry. Such strong relationships are (to our knowledge) not yet described in the literature. On the contrary, the existence of several double dissociations between tasks assumed to reflect the operation of the MNL (e.g., Rossetti et al., 2004; Doricchi et al., 2005, 2009; Loetscher and Brugger, 2009; Loetscher et al., 2010; van Dijck et al., 2009, 2011), suggest that the internal structure of number–space is characterized by more than one component. In line with this idea, neglect in number–space is considered as a form of representational neglect (e.g., Umiltà et al., 2009), which is known to be dissociable from physical neglect (e.g., Guariglia et al., 1993). Although not necessarily in contradiction with this latter position, the PCA conducted in the present study extracted three components, thereby supporting the idea that even more cognitive mechanisms are involved in the realization of the interaction between numerical and spatial processing. Furthermore, as will be illustrated next, the obtained pattern of component loadings captures the dissociations described in the literature. Together, this provides useful information to come to an understanding of the nature of the underlying mechanisms.

Although the group analyses showed a joint bias between physical line bisection and number interval bisection, both tasks did not share the same component. This suggests that the attentional asymmetry in physical space is not associated with the bias in number interval bisection. This conclusion is strengthened by the observation that in our sample, interval bisection and physical line bisection were double dissociated in some patients. Similar observations were made by Doricchi et al. (2005, 2009), who in addition reported that the deficit in number interval bisection can be attributed to a problem in the retention of spatial and verbal sequences. In line with this idea, interval bisection significantly loaded on two other components, one shared with the magnitude comparison SNARC-effect, and one with parity judgment SNARC-effect and the asymmetry index of the distance-effect.

The classic explanation of the SNARC-effect is that it arises from a correspondence between the position of the number on the MNL and the position of the response, irrespective of the task used to obtain it (e.g., Dehaene et al., 1993). It has been proposed that in tasks where numerical magnitude is used explicitly, neglect should hamper access to the left side of this representation (Priftis et al., 2006). In contrast to this prediction, both the parity judgment (where numerical magnitude is not needed to solve the task) and magnitude comparison SNARC-effects of the present study were unaffected by neglect. This observation confirms alternative accounts on the SNARC-effect which propose conceptual spatial representations as the determining factor of the SNARC-effect, rather than perceptual spatial representations. For example Proctor and Cho (2006) assume that space, like many other cognitive representations, is organized in binary categories (e.g., left/right; small/large; hot/cold). Moreover, such conceptual categories have a polarity (e.g., left is negative and right is positive; small is negative and right is positive;. . .) and it is the correspondence between the polarity of the stimulus (viz. the magnitude of the number) and the response (viz. position of the response) that induces the SNARC-effect (for a similar account see Gevers et al., 2006; Santens and Gevers, 2008). Given the observation that conceptual and perceptual spatial representations rely on dissociable neural systems (Jager and Postma, 2003), it is no surprise that both SNARC-effects are spared in neglect.

This explanation however, is not complete as it does not account for the fact that both effects also differ from each other: whereas in parity judgment the effect was similar in all subjects, in magnitude comparison it was considerably larger in the patient groups. These observations are captured by our PCA, which extracted separate components for these tasks, indicating that both effects are associated with different cognitive processes. A possible explanation for this finding was recently proposed by the computational model of the relation between numbers and space (Chen and Verguts, 2010). This model proposes two independent sources for the SNARC-effect, one depending on conceptual congruency, and one on the use of visuo-spatial resources (probably via the use of mental imagery). The existence of those two sources was recently confirmed by van Dijck et al. (2009) who found that both SNARC-effects had a different origin. When neurologically intact subjects were asked to memorize verbal information while judging the parity status of numbers, the SNARC-effect disappeared, whereas the effect remained untouched under a spatial working memory load. In magnitude comparison, however, the opposite was observed (see also Herrera et al., 2008). Here the SNARC-effect vanished under spatial but not under verbal working memory load. Based on these observations, they concluded that numbers are associated with visuo-spatial or verbally mediated spatial codes, and that magnitude comparison and parity judgment engage these codes differentially.

When considering the results of the PCA, the number of components extracted together with their loading profiles, fit with the findings described above. Indeed, where the involvement of visuo-spatial working memory has been demonstrated in both number interval bisection (Doricchi et al., 2005) and the magnitude comparison SNARC-effect (Herrera et al., 2008; van Dijck et al., 2009), both effects load on the same component. Similarly, both the number interval bisection (Doricchi et al., 2009; van Dijck et al., 2011) and the parity judgment SNARC-effect (van Dijck et al., 2009; van Dijck and Fias, 2011) are previously associated with verbal working memory, and also load on the same component. At present however, the exact and detailed role of those working memory resources needs further experimentation and computational modeling work. For example, in the model of Chen and Verguts (2010), the involvement of spatial working memory has been interpreted in the context of mental imagery which is used to construct a spatial representation when solving certain tasks involving numbers. For both number interval bisection and for magnitude comparison, the use of spatial imagery can indeed be helpful to efficiently solve the task. In that sense, the independence of this spatial imagery component from the component involving physical line bisection could reflect the dissociation between physical and representational neglect as proposed by Umiltà et al. (2009). The role of verbal working memory, however, is at present less well understood (and not yet explicitly modeled). One possible explanation has recently been described by Fias and colleagues (Fias et al., 2011; van Dijck and Fias, 2011), who proposed that the parity judgment SNARC-effect is a reflection of the way numbers are mentally organized in verbal working memory. In a series of experiments, they asked participants to perform a parity judgment task on numbers that were maintained as a randomly ordered sequence in working memory. It was observed that it was the position of the number in this memorized sequence but not its numerical magnitude that determined the spatial coding of the number (viz. begin elements were associated with a left response, and end elements with a right one). A similar role of verbal working memory in number interval bisection has recently been proposed by van Dijck et al. (2011). They described a woman suffering from left hemisphere brain damage, who showed a double dissociation between right physical and representational neglect on the one hand, and left neglect for numbers, and other ordered sequences on the other hand. Further neuropsychological examination revealed that this seeming left sided neglect had a pure non-spatial origin and was based on defective memory for the initial items of verbal sequences. From this, they concluded that for efficient number interval bisection, the entire range of numbers comprising the interval needs to be collected and correctly ordered in verbal working memory. If the shared component is indeed reflecting the involvement of verbal working memory, those results suggest that the explanation proposed in this single case study can be generalized to the population, to explain at least a part of the variance of the interval bisection data.

In addition, the results also speak to the cognitive origin of the asymmetry of the distance-effect and how it relates to the other effects. While this effect became asymmetrical in neglect, the SNARC-effect obtained in the same task remained unaffected. This dissociation was again captured by the PCA, which associated both effects with different components. The dissociation between the distance-effect and the SNARC-effect has been reported previously. Herrera et al. (2008) and van Dijck et al. (2009) observed that in neurologically intact subjects, a spatial working memory load reduced the SNARC-effect, leaving the distance-effect unaffected. Both findings together provided strong evidence that both effects are indeed independent (see also Gevers et al., 2006; Chen and Verguts, 2010). Interestingly, the asymmetry index of the distance-effect is the only number–space signature in the present study that shares a component with physical line bisection, suggesting that the effect is mediated by spatial attention. In support of this idea, in the model of Chen and Verguts (2010) the asymmetry of the distance-effect is indeed the only effect for which damage to the attentional mechanisms of the right hemisphere should be sufficient to obtain it. It is remarkably, however, that again not all neglect patients showed an asymmetrical distance-effect. This can probably be explained by the fact that this effect also loads on the component shared with interval bisection and parity judgment SNARC-effect. Given the descriptions above, this finding suggest that the asymmetry index of the distance-effect also draws upon verbal resources. Interestingly, the component loading is reversed in sign compared to that of the parity judgment SNARC-effect and the interval bisection bias. If, like van Dijck et al. (2011) propose, verbal working memory resources are important to encode the ordinal relations between numbers, one would predict that such resources are also of relevance when comparing numbers with a fixed standard. A reduction of such resources would thus not only affect interval bisection and parity judgment, but also number comparison, and its associated distance-effect. It is obvious that when the distance-effect decreases due to a lack of verbal resources, its asymmetry will do so correspondingly. Whether or not the distance-effect depends on verbal resources is a matter of future investigations, and to our knowledge, no direct evidence for this position is described in the literature. Indirectly however, it is remarkable that in the second experiment described by Herrera et al. (2008), where the magnitude comparison task is administered under verbal and spatial working memory load, the overall reaction times increased selectively in the verbal load condition.

The question remains why we found a magnitude comparison SNARC-effect in neglect patients, while no such effect was found by Vuilleumier et al. (2004). Although speculative, this difference can be related to differences in the counterbalancing of the response mapping. In magnitude comparison, where SNARC-congruency changes block wise, it is important to ensure that the effect is not attenuated by learning effects [e.g., when a subject have to start with the compatible response mapping (small → left, large → right), RT's of this condition can be higher due to time needed to get used to the experimental setup and the response device, in extreme cases masking the presence of a SNARC-effect]. For this reason it is of importance to properly counterbalance the response mapping of this task, especially when investigating elderly subjects who are often not very familiar with computerized response devices. No information of such counterbalancing has been provided by Vuilleumier et al. (2004), making it possible that the used counterbalancing scheme gave rise to the pattern of data they described. In our study on the other hand, the counterbalancing of the response mapping (and also the order in which both SNARC-tasks are presented) is controlled for, making it more likely to observe the actual effect.

Finally, it is important to emphasize that the results of the PCA are truly reflecting different components of number–space interactions, rather than general task differences. The reason is that we entered the behavioral effects as signatures of number–space interactions (SNARC-effect, bisection bias, asymmetry of the distance-effect) rather than the reaction times themselves. This guarantees that the PCA components reflect number-specific processing rather than general task factors like perceptual processing, the type of decisions that has to be made, the way responses are collected etc. In support of this idea, it is important to note that the pattern of loadings obtained in the PCA fits closer the theoretical interpretations derived from previously found dissociations and associations, than just task differences. For example, the asymmetry index of the distance-effect and the magnitude comparison SNARC-effect, which are obtained from the same task and data are not assigned to the same component, which would have been expected if the PCA would have extracted general task differences.

In conclusion, the results of the present study show that the MNL is insufficient to capture the variety of number–space interactions measured across different tasks. Instead of one single underlying representation associated with external space, the present study shows that at least two additional independent components, related to spatial and verbal working memory, are characterizing the internal structure of the "number–space." How other tasks and effects (e.g., Rossetti et al., 2004; Stoianov et al., 2008; Salillas et al., 2009; Cattaneo et al., 2011; Kramer et al., 2011) that are assumed to be related to number–space interactions are situated with respect to the presently identified components is a matter of further investigation and cannot be determined *a priori.* We are convinced however that the components described in the present study can be considered as a first step toward a new unitary framework for understanding of the relation between numerical and spatial processing in general.

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Neglect impairs explicit processing of the mental number line

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Converging evidence suggests that visuospatial attention plays a pivotal role in numerical processing, especially when the task involves the manipulation of numerical magnitudes. Visuospatial neglect impairs contralesional attentional orienting not only in perceptual but also in numerical space. Indeed, patients with left neglect show a bias toward larger numbers when mentally bisecting a numerical interval, as if they were neglecting its leftmost part. In contrast, their performance in parity judgments is unbiased, suggesting a dissociation between explicit and implicit processing of numerical magnitude. Here we further investigate the consequences of these visuospatial attention impairments on numerical processing and their interaction with task demands. Patients with right hemisphere damage, with and without left neglect, were administered both a number comparison and a parity judgment task that had identical stimuli and response requirements. Neglect patients' performance was normal in the parity task, when processing of numerical magnitude was implicit, whereas they showed characteristic biases in the number comparison task, when access to numerical magnitude was explicit. Compared to patients without neglect, they showed an asymmetric distance effect, with slowing of the number immediately smaller than (i.e., to the left of) the reference and a stronger SNARC effect, particularly for large numbers. The latter might index an exaggerated effect of number-space compatibility after ipsilesional (i.e., rightward) orienting in number space. Thus, the effect of neglect on the explicit processing of numerical magnitude can be understood in terms of both a failure to orient to smaller (i.e., contralesional) magnitudes and a difficulty to disengage from larger (i.e., ipsilesional) magnitudes on the number line, which resembles the disrupted pattern of attention orienting in visual space.

Keywords: neglect, spatial attention, mental number line, SNARC effect, distance effect, mixed effects models

INTRODUCTION

Interactions between numbers and space are a major issue in numerical cognition research. The dominant view posits that numerical representations are rooted in cortical networks that also subserve spatial cognition (for reviews, see Walsh, 2003; Hubbard et al., 2005; Umiltà et al., 2009). A more specific hypothesis is that numbers are represented as local activations (points or regions) along a spatially oriented *mental number line* (Dehaene et al., 1993; Zorzi et al., 2002; Dehaene, 2003; also see Moyer and Landauer, 1967, and Restle, 1970, for earlier proposals of mental number line). Spatial coding of numbers would be at the core of number meaning because number magnitude is conveyed by its position on the number line (Dehaene, 2003). The spatial orientation of the number line is influenced by cultural factors (Göbel et al., 2011, for review), and in Western cultures it conforms to a left-to-right (and small-to-large) horizontal layout (Dehaene et al., 1993; Zorzi et al., 2002).

The strongest evidence supporting the number line hypothesis comes from neuropsychological studies on patients with left hemispatial neglect, who following a lesion of the right hemisphere fail to report, orient to, or verbally describe stimuli in the contralesional left hemispace (Halligan et al., 2003, for a review). When asked to mark the midpoint of a visual line, neglect patients systematically displace it to the right of the true midpoint, as if they ignore the leftmost part of the line. The rightward displacement is, in most patients, directly proportional to the length of the segment, but for very short segments a paradoxical leftward displacement of the midpoint is typically observed (i.e., the crossover effect). Note that neglect is not confined to stimuli that are actually present in the environment, but extends, in some patients, also to mental imagery (e.g., Bisiach and Luzzatti, 1978). For example, the bisection bias was also observed when neglect patients had to bisect imagined lines (e.g., Bisiach et al., 1994). Zorzi et al. (2002) reasoned that if the number line were a representation with a truly spatial nature rather than a mere metaphor (as hitherto believed), neglect patients would show a bias in mentally bisecting a numerical interval that would resemble the one they show in the line bisection task. Indeed, patients with left neglect in physical space systematically misplaced the midpoint of an orally presented numerical interval (e.g., responding that 5 is halfway between 2 and

6) and their errors closely resembled the typical pattern found in the bisection of visual lines, including the modulating effect of line length and the crossover effect with very short numerical intervals. The finding that neglect affects "number space" was replicated and extended in a number of subsequent studies (e.g., Rossetti et al., 2004; Vuilleumier et al., 2004; Doricchi et al., 2005; Priftis et al., 2006, 2008; Zorzi et al., 2006; Cappelletti et al., 2007; Zamarian et al., 2007; Hoeckner et al., 2008; Salillas et al., 2009). Converging evidence is also provided by studies on healthy participants that investigated rTMS-induced neglect (Göbel et al., 2006) and pseudoneglect (Longo and Lourenco, 2007).

The findings on number interval bisection in neglect patients led Zorzi et al. (2002) to propose a functional isomorphism (or homeomorphism) between the mental number line and visual lines, which has been recently referred to as the "strong version" of the number line hypothesis (Fias et al., 2011; van Dijck et al., 2011). It is important to emphasize, however, that Zorzi et al. did not claim that the number line is represented as a visual line. Two spaces are homeomorphic if they have the same topology; in the present context, this notion implies that the number line and visual lines have the same spatial metrics, but it does not require any common representation or shared neural mechanism. In turn, this implies that dissociations between the number space and other (perceptual or imaginary) spaces can occur (e.g., Rossetti et al., 2004; Zorzi et al., 2004; Doricchi et al., 2005; Loetscher and Brugger, 2009; Loetscher et al., 2010; van Dijck et al., 2011; see Rossetti et al., 2011, for review). Note that these dissociations are not surprising because they mirror and extend to the number space the well known double dissociation between imaginal and perceptual space in neglect patients (Anderson, 1993; Guariglia et al., 1993). It would be odd to maintain that, as a consequence of the latter dissociation, imaginal neglect should not be considered as spatial in nature, or that the imaginal space is not isomorphic to the perceptual space (for example, the patient's mental image of her own bedroom has indeed the same spatial metrics and coordinate system of the actual bedroom). We believe that the same logic should hold for the dissociation between neglect for physical space and neglect for the number space. All these dissociations within neglect can be explained by the fact that the brain creates a variety of spatial representations implemented within distinct neural circuits and that a unitary, supramodal spatial attention system does not exist (Rizzolatti and Berti, 1993; Casarotti et al., 2012).

The effect of hemispatial neglect should not be conceived as a literal "disruption" of the number space, but as a failure in orienting to or exploring one portion of that space due to impaired attentional mechanisms, just as it is the case for visual space and for other imaginal spaces. Indeed, Priftis et al. (2006) found that left neglect affected numerical processing when the task required an explicit processing of numerical magnitude, as in the number interval bisection task (or in number comparison; Vuilleumier et al., 2004), but not when processing was implicit, as in parity judgments. The dissociation between implicit and explicit processing of contralesional information is a solid (and intriguing) phenomenon in the neuropsychological literature of neglect (see Berti, 2002, for review). Recently, Treccani et al. (2012) observed that neglected stimuli can produce spatial correspondence effects, suggesting that the spatial representation of the contralesional side is intact, but cannot be explicitly accessed. Within the numerical domain, this dissociation clearly supports the hypothesis that neglect affects the allocation of spatial attention over an intact number line (Priftis et al., 2006).

A complementary observation regarding the effect of neglect on numerical magnitude access was made by Vuilleumier et al. (2004) using the number comparison task. They found that neglect patients were abnormally slow in responding to the number immediately smaller than (that is, to the left of) the reference number. For instance, when the reference number was "5," responses to "4" were much slower than responses to "6," though both have the same numerical distance from the reference. In contrast, the performance of right brain damaged patients without left neglect and healthy controls was characterized by a regular, symmetric distance effect (Moyer and Landauer, 1967). When the reference number changed to "7," neglect patients became slower in processing "6," which is again the number immediately to the "left" of the reference. Thus, the same number was processed faster or slower depending on its spatial position relative to the reference number. Moreover, when Vuilleumier and colleagues asked their participants to think about numbers as being clock hours, neglect patients became selectively slower in responding to larger numbers, which are represented on the left part of the clock face. This remarkable flexibility in changing reference frame for the spatial coding of numbers fits well with the seminal findings of Bisiach and Luzzatti (1978) on representational neglect, whereby the neglected side of a mental image depends on the (imagined) subjective viewpoint of the patient (see also Bachtold et al., 1998). More recently, Salillas et al. (2009) presented right brain damaged patients with and without neglect with digits in the 1–4 and 6–9 ranges. Patients were asked to respond to the digit only if its magnitude was smaller (or larger, in a different block) than the reference ("5"). A selective slowing for the digit immediately smaller than the reference emerged for neglect patients, as in Vuilleumier et al.'s (2004) study. Moreover, Salillas et al. showed that this slowing was significantly reduced when a pattern of leftward-moving dots was presented on the screen. That is, coherent dot motion, which is known to induce shifts of visuospatial attention congruent with the direction of motion, influenced performance in number comparison ameliorating neglect for number space.

The earliest reaction time (RT) evidence for interactions between numbers and space in healthy participants was provided by Dehaene et al. (1993; also see Dehaene et al., 1990), who discovered the Spatial-Numerical Association of Response Codes (SNARC) effect. It consists in faster left-sided responses to small than to large numbers and in faster right-sided responses to large than to small numbers. The SNARC effect is another demonstration of the remarkable flexibility of spatial coding, because the association of a given number with "left" or "right" is not absolute but relative to the tested number range (Dehaene et al., 1993). The classic interpretation of the SNARC effect is that it indexes spatial correspondence (i.e., corresponding vs. non-corresponding trials), between position of the number on the number line and position of the response (but see Gevers et al., 2006; Proctor and Cho, 2006; Gevers et al., 2010; also see General Discussion). The SNARC effect can be induced with various effectors, such as hands, fingers of the same hand (Priftis et al., 2006), feet (Schwarz and Müller, 2006), and saccades (Fischer et al., 2004; Schwarz and Keus, 2004). The effect can be observed both in magnitude comparison and in parity judgments of Arabic digits. Note that the presence of a SNARC effect during parity judgments indexes automatic (or implicit; Priftis et al., 2006) access to numerical magnitude (Dehaene et al., 1993), because the latter is task-irrelevant. There is only one published study that focused on the SNARC effect in neglect patients. Priftis et al. (2006) found that left neglect patients, who were impaired at number interval bisection, showed a regular SNARC effect in the parity judgment task that did not differ from that of healthy controls. Also the study of Vuilleumier et al. (2004) included a manipulation of the response-key assignment in number comparison (i.e., "larger" response on the left vs. right side) that would allow to assess the SNARC effect. The latter, however, was not the focus of their study. Vuilleumier and colleagues reported that the incompatible mapping was generally slower and more error-prone. Although the type of mapping did not interact with group in the main analyses, neglect patients did not show slower responses in the incompatible mapping, as if they failed to show a regular SNARC effect. Nevertheless, performing the incompatible mapping turned out to be too difficult for some neglect patients.

It is worth noting that several types of associations between numbers and space (often variants of the SNARC effect) have been reported by a wealth of behavioral studies on healthy participants. Their review is clearly beyond the scope of the present article, but a few studies are particularly relevant in the present context because they directly speak in favor of attention-mediated interactions between the perceptual space and the number space. For instance, the involvement of visuospatial attention in number processing is clearly supported by the finding that numerical cues can orient attention in visual space (e.g., Fischer et al., 2003; Casarotti et al., 2007; Cattaneo et al., 2009). Accordingly, the rightward bias shown by neglect patients in visual line bisection can be modulated by task-irrelevant digit flankers ("1" leftwards and "9" rightwards; Bonato et al., 2008). Even more important is the demonstration of interaction in the opposite direction, with visuospatial processing influencing number processing, thereby showing that the spatial aspects of numerical processing are not epiphenomenal. Stoianov et al. (2008; also see Kramer et al., 2011) found that an irrelevant visuospatial cue primes a target number in both magnitude comparison and parity judgments. That is, responses (which were vocal and non-spatial) were faster for small than for large numbers when the prime was a left-sided visual cue and faster for large than for small numbers when the prime was a right-sided visual cue. A similar effect was found by Nicholls and McIlroy (2010) for number interval bisection. Finally, mental calculation also seems to be related to a spatial representation of numbers. One clear example is the "Operational Momentum" (OM) effect (McCrink et al., 2007). When asked to add or subtract large sets of dots (see also Knops et al., 2009a), participants underestimated the result of subtractions ("leftward" bias on the mental number line), whereas they overestimated the results of additions ("rightward" bias) in analogy with the "representational momentum" found when the spatial position of a moving object has to be estimated (Freyd and Finke, 1984). The hypothesis that mental calculation involves shifts of spatial attention along the number line (Hubbard et al., 2005) has found direct support in a recent fMRI study: Knops et al. (2009b) observed that the pattern of brain activation in the posterior superior parietal cortex resembled the activation found for rightward saccades when additions were performed and that for leftward saccades when subtractions were performed.

The main aim of the present study was to further investigate the influence of an impairment of visuospatial attention (neglect) on number processing and its interaction with task demands, with specific reference to the distinction between implicit and explicit access to numerical magnitude. As noted before, Priftis et al. (2006) interpreted the dissociation between spared SNARC effect in parity judgment and impaired number interval bisection in terms of the implicit vs. explicit nature of the two tasks. This hypothesis leads to the prediction that the SNARC effect in number comparison should be affected by neglect, because number comparison implies the explicit processing of numerical magnitude. Therefore, we sought to establish whether the SNARC effect in number comparison is affected by neglect and whether the same patients display a normal SNARC effect in parity judgments. The performance of right brain damaged patients with neglect was assessed against that of control patients with right hemisphere damage, but without neglect. Importantly, our contrast between explicit and implicit tasks is much more stringent than in Priftis et al.'s study, because our number comparison task (unlike their number interval bisection task) was identical to the parity judgment task both in terms of stimuli (i.e., a single digit presented at fixation) and response requirements (i.e., key-press responses using the index and middle fingers of the right hand; switch of the response-key assignment). Our approach is, therefore, clear-cut: Any difference in performance between the two tasks must be attributed to the way in which stimulus information is internally processed to accomplish the task. Moreover, given that the two groups of patients differed only for the presence of neglect, any difference between groups must be ascribed to an impaired orienting of visuospatial attention. Finally, our study allowed us to reassess the asymmetry of the distance effect observed by Vuilleumier et al. (2004) in neglect patients, which has only one published replication to date (Salillas et al., 2009). We also assessed whether the selective slowing of "4" during comparison (with reference 5) disappears during parity judgment, as predicted by the explicit vs. implicit account.

MATERIALS AND METHODS

PARTICIPANTS

Twenty patients with a brain lesion affecting the right hemisphere, confirmed by CT of MR scan, participated in the study. Patients were included in the present study for the presence of right hemisphere damage affecting frontal, temporal, parietal, or subcortical areas, independently from its etiology (e.g., vascular or neoplastic). Patients were all right-handed and were affected by mild to severe motor deficits in the left hemibody. They were admitted to a rehabilitation center to undergo motor rehabilitation for left hemiplegia/hemiparesis. All patients gave written informed consent to participate in the study. None of them had positive medical history of previous neurological disease or substance abuse. The study adhered to the principles of the Declaration of Helsinki.

NEUROPSYCHOLOGICAL TESTING

All patients were initially tested with the Mini-Mental State Examination (MMSE; Magni et al., 1996). This was followed by a thorough assessment with a comprehensive neuropsychological battery (ENB; Mondini et al., 2003). Finally, the conventional part of the Behavioral Inattention Test (BIT; Wilson et al., 1987) was administered to investigate the presence of peripersonal neglect. BIT is a battery that includes different subtests: barrage, letter cancellation, star cancellation, bisection, coping, and drawing from memory tests. According to the score obtained on the BIT, twelve patients were assigned to the neglect group (N+) and eight patients to the group without neglect (N−).

In the analysis of the computer-based task we excluded patients who had a mean error rate ≥25% in at least one of the two response-key assignments (see below), failed to accomplish with instructions, or did not complete the task. Following the application of these criteria, data from seven N− patients were analyzed for both parity and comparison tasks. For the N+ group, the data of five patients were analyzed for both parity and comparison tasks, one patient entered only in the comparison task and one patient only in the parity task. **Table 1** shows demographic data and test scores for the patients who entered the analysis (7 N− and 7 N+).

The two groups (7 N+ and 7 N−) did not significantly differ in age, $F(1, 12) = 3.66$, $p = 0.08$ (mean N+ 73 years, SD 7.2; N− 65 years, SD 8.9), education, $F(1, 12) = 0.96$, $p = 0.35$ (mean N+ 7.1 years, SD 4.5; N− 5.4 years, SD 1.1), or time from lesion, $F(1, 12) = 0.33$, $p = 0.58$ (mean N+ 379 days, SD 838; N− 178 days, SD 398). The overall BIT score was significantly different between the two groups, $F(1, 12) = 12.06$, $p < 0.01$, with a mean score higher for N− (140, SD 4.1) than for N+ (94, SD 34.6). All BIT subtest scores, except for line cancellation, were significantly lower in N+ with respect to N− (all ps < 0.05). The scores for neuropsychological tests did not differ between N+ and N− when the task did not heavily rely on visuospatial abilities (e.g., MMSE, Digit Span, memory for a story in both immediate and delayed recall, memory with interference subtests (10 s version), verbal fluency, abstraction, cognitive estimation, ideomotor praxis). In contrast, the scores for neuropsychological tests differed between N+ and N− (all ps < 0.05) when the task demanded the use of visuospatial abilities (e.g., copy of drawing, drawing from memory – flower and clock, overlapping figures). The TMT (in both versions) was too difficult for N+ patients and most of them failed to complete the test within the time limit.

PROCEDURE

Patients were asked to classify a single digit (1–4 and 6–9) as smaller or larger than the reference 5 (Comparison task) or as odd or even (Parity task). Following Priftis et al. (2006), patients executed their responses only with their right (non-plegic) hand, using the index and middle fingers (Unilateral SNARC Paradigm). The experimenter aligned the trunk midline of each participant with the left border of the computer screen. The viewing distance was about 60 cm. Each trial started with a blank screen, which was followed after 500 ms by a fixation cross that lasted for 1000 ms. Then an additional blank screen was presented for 500 ms, which was followed by the target digit displayed at fixation until response. Acoustic feedback (a low-frequency tone) was provided for 1000 ms following incorrect responses. At the end of each trial, the word "ready" was displayed until the experimenter pressed a button on a separate keyboard to start the next trial. The inter-trial interval was 500 ms.

The experimental manipulation for observing a SNARC effect consists in switching the response-key assignment (e.g., left response for odd numbers in the parity task) after half of the trials, such that each number is responded to with both the left and the right effector (Dehaene et al., 1993). However, as first noted by Vuilleumier et al. (2004), switching response mapping can be extremely difficult (if not impossible) for some patients. Indeed, neglect patients in Priftis et al.'s (2006) study performed the two mappings of the parity task in separate sessions (days). Accordingly, we employed the same strategy of switching response mapping (within the same task) in separate sessions: each session included both parity and comparison tasks, either with a compatible or incompatible mapping. The compatible mapping was defined in terms of magnitude for the comparison task (left response for small and right response for large numbers; i.e., SNARC compatibility; Dehaene et al., 1993) and in terms of parity status for the parity task (left response for odd and right response for even, that is MARC compatibility; Nuerk et al., 2004). For each task and mapping, two blocks with 64 trials each were presented. Task order (e.g., parity or magnitude first) and response mapping (e.g., compatible or incompatible first) were counterbalanced across participants.

Control (N−) patients performed two sessions. Neglect patients performed four sessions with the exception of patients RR, who performed only two sessions, and TM, who performed only the comparison task (in two sessions). Neglect patients' testing occurred in two consecutive days, in two consecutive weeks (e.g., Monday–Tuesday of week 1 and Monday–Tuesday of week 2). Thus, all neglect patients (except TM and RR) performed 512 trials in the magnitude and 512 trials in the parity task. All patients without neglect performed 256 trials in the magnitude and 256 trials in the parity task. Increasing the number of trials in neglect patients was necessary because the task was difficult for most of them (which implies more variability in performance). This allowed us to obtain a more robust dataset.

RESULTS

Trials with RTs faster than 200 ms and slower than 4500 ms in either task were classified as outliers and excluded from analyses. **Table 2** shows the descriptive statistics for RTs and error rates, separately for each task (Number Comparison or Parity Judgment) and group (N− or N+). We analyzed correct RTs of both the comparison and parity tasks with *linear mixed effects models* (see Baayen, 2008; Baayen et al., 2008), implemented with lme4 (Bates et al., 2008) and language R packages (Baayen, 2008). These models are based on single trial data rather than on averaged data, and allowed estimating the genuine effects of the variables under investigation (i.e., fixed effects; e.g., group, SNARC compatibility, distance, etc.) and separating these effects from those of other spurious variables (i.e., random effects), such as individual variability, general response slowing, block order effects, and so on.

Table 1 | Demographic data and test scores of right brain damaged patients with neglect (N+) and without neglect (N−).

Group	N+	N+	N+	N+	N+	N+	N+	N−	N−	N−	N−	N−	N−	N−
Sex (male–female)	M	F	M	F	M	F	M	F	M	M	F	M	M	M
Age (years)	81	62	77	74	65	80	73	67	69	47	76	65	67	63
Education (years)	5	13	5	1	8	5	13	5	8	5	5	5	5	5
Time from onset (days)	34	27	57	122	52	85	2278	1081	56	41	31	12	18	9
Etiology	I	I + T	H	I	I	I	H	I	I	T	I	T	I	I
Lesion site	Si, BG	F, T, P	Th, IC	F, T	F, T, P	Si	BG	PV	F, T, P	F, P, CG	PV, BG	P	PV	BA
MMSE	24	27	24	22	27	22	27	26	29	26	24	28	26	28
BIT tot	39	90	60	96	129	121	126	140	138	143	134	143	137	146
BIT SUBTESTS														
LINE canc. (CoC)^	0.66	0.06	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
STARS canc. (CoC)	0.84	0.38	0.57	0.50	0.04	0.02	0.01	0.02	−0.01	0.00	0.01	0.00	0.00	0.00
LETTERS canc. (CoC)	0.84	0.04	0.01	0.15	−0.02	0.30	−0.05	−0.04	−0.01	0.01	0.00	−0.01	−0.03	0.00
COPY (tot)°	1	1	2	2	4	3	3	4	4	4	3	3	3	4
BISECTION (tot) §	2	5	1	3	6	5	6	9	9	9	9	9	9	9
DRAW (tot)°	1	1	1	3	1	1	3	3	2	3	3	3	2	3
ENB SUBTESTS														
Digit span	6	6	4	6	5	4	7	4	4	4	5	6	4	7
Story: immediate recall	8	9	9	9	13	10	15	8	12	5*	14	14	9	4*
Story: delayed recall	13	10*	9	13	12	9	17	11	15	9*	20	12	12	7*
Memory + interf. (10s)	3	0*	3	6	4	4	5	3	0*	3	8	6	5	3
Memory + interf. (30s)	2*	4*	3	3	3	3	4*	3*	5	7	8	8	6	3*
Trail making test A (s)	ne*	65	ne*	ne*	195*	ne*	70	73	69	41	29	38	87	132*
Trail making test B (s)	ne*	ne*	ne*	ne*	ne*	ne*	270*	256*	312*	312*	131	100	ne*	143
Token test	3*	5	5	5	5	5	5	5	4.5*	5	5	5	4*	4.5*
Fluency (phonemic)	9.3	6.7*	5.7	4.3*	5.7*	4*	4.7*	6.7*	5.7*	9.3	11.7	5.3*	6*	8.7
Abstract reasoning	3	6	4	0*	6	2*	4	4	6	2*	6	5	2*	2*
Cognitive estimation	4	3*	5	3*	4	2*	3*	4	5	3*	4	5	4	4
Overlapping figures	3*	20*	2*	15*	13*	5*	14*	22*	21*	24*	32	23*	19*	22*
Copy of drawing	0*	0*	0*	0*	1*	1*	1*	1*	1*	1*	2	1*	2	2
Spontaneous drawing	0*	2	1*	0*	1*	2	0*	2	2	2	2	2	2	2
Clock drawing	1.5*	2*	9	1.5*	1.5*	4.5	10	10	8.5	9.5	10	10	9.5	9.5
Ideomotor praxis	5*	6	6	6	6	5*	6	6	6	6	6	6	6	4*

Lesion site: Si, silvian; F, frontal; P, parietal; T, temporal; IC, internal capsule; CG, cingulate gyus; BG, basal ganglia; Th, thalamus; PV, periventricular; BA, basal artery. Etiology: I, ischemic; H, hemorrhagic; T, tumor.

^CoC: Center of Cancellation (Rorden and Karnath, 2010), with 0 indicating perfect symmetry (i.e., center of the sheet) and 1 cancellation limited to the right-most targets.

°One point is given for each task (four copying and three drawing tasks) if performance does not reveal important asymmetries.

§Bisection of each of the three lines in the subtest is scored from 0 to 3 according to the accuracy of performance.

**Altered performance (score below the 5th percentile with respect to the performance of matched controls).*

ne, not executed (not finished within the allowed time).

This novel approach is particularly interesting for the analysis of patients' RT data, which are typically more noisy than the RT data of healthy participants. We also performed a series of follow-up analyses using more conventional methods (regressions and t-tests; Fias et al., 1996).

MIXED EFFECTS MODELS

Separate models were fitted to the comparison RTs and the parity RTs. For both tasks, we first defined a model with participants as a random effect. Then, we entered in the model(s) the interaction between participants and the part of the experiment to which the trial belonged (i.e., part one comprised the first two sessions, whereas part two comprised the following two sessions, when performed) – that is, the effect of the experimental part was allowed to vary between participants. A log-likelihood test was performed (here and at each successive step) to determine if the improvement in the model's fit was significant, $\chi^2(2) = 27.6$, $p < 0.0001$ for comparison task and $\chi^2(2) = 59.80$, $p < 0.0001$ for parity task. In a third step we added the interaction between participants and the experimental block, whereas in a fourth step we included the interaction between participants and the ordinal position of the trial within the block. Both steps yielded

Table 2 | Descriptive statistics for RTs and error rates, as a function of task and group.

		Mean	Min	Max	SD
RT (MS)					
N+	Number comparison	1071.5	673.6	1301.0	225.1
	Parity judgment	1054.8	664.0	1304.3	229.3
N−	Number comparison	679.6	534.8	949.2	131.0
	Parity judgment	735.3	589.7	1002.4	160.2
ERROR RATE (%)					
N+	Number comparison	5.00	1.36	8.78	3.24
	Parity judgment	5.03	1.16	12.68	4.19
N−	Number comparison	5.34	0.78	13.25	4.13
	Parity judgment	8.24	3.11	14.43	4.43

Mean, minimum, maximum, and standard deviations are reported.

significant improvements in the models' fits, all χ^2s ≥ 32.19, all $ps < 0.0001$. We then entered as fixed effects all factors (and their interactions) that could influence performance in the two tasks: SNARC compatibility (compatible or incompatible mapping between digit magnitude and response side, i.e., small-left and large-right vs. large-left and small-right), MARC compatibility (compatible or incompatible mapping between digit parity and response side, i.e. odd-left and even-right vs. even-left and odd-right), the participant's group (i.e., N+ vs. N−), the magnitude of the target with reference to 5 (i.e., larger vs. smaller than 5), and the numerical distance between target and reference (i.e., 1–4).

Comparison task

In the analysis of the comparison data, introducing SNARC compatibility yielded a significant improvement of the model's fit, $\chi^2(1) = 37.52$, $p < 0.0001$. We then added the interaction between SNARC compatibility and the participant's group (i.e., N+ vs. N−). Importantly, this interaction improved significantly the model's fit, $\chi^2(2) = 16.45$, $p < 0.0005$. Moreover, the interactive model had a better fit than the model with SNARC compatibility and group as additive factors, $\chi^2(1) = 5.44$, $p < 0.05$, thereby showing that the magnitude of the SNARC effect was larger in neglect patients than in control patients (mean difference between incompatible and compatible trials: 257 ms for N+ vs. 80 ms for N−). MARC compatibility, as well as its interaction with group, failed to yield any improvements in model's fit, both χ^2s ≤ 0.03, $p = 0.98$. We then added to the model in successive steps the magnitude of the target with reference to 5 (i.e., larger vs. smaller than 5), and the numerical distance between target and reference (i.e., 1–4). The comparisons between fits obtained at both steps showed significant improvements, both χ^2s ≥ 5.05, both $ps \leq 0.05$. In the next step we added the interaction between distance and magnitude. A significant improvement in the model's fit, $\chi^2(1) = 7.93$, $p < 0.005$, suggested that the distance effect was asymmetric (i.e., different distance effects for numbers smaller and larger than 5). We therefore tested for the significance of the interaction between distance, magnitude and group. The (final) model including this three-way interaction (AIC = 66178, BIC = 66305, Log-Likelihood = −33069) showed a better fit, $\chi^2(3) = 32.66$, $p < 0.0001$, thereby showing that the asymmetry of the distance effect for small and large numbers differed between the two groups. None of the other interactions between the fixed factors, when added to the final model, resulted in a significant improvement in the model's fit, all $\chi^2 \leq 2.45$, all $ps \geq 0.38$.

Parity task

In the analysis of parity RTs, MARC compatibility significantly improved the model's fit, $\chi^2(3) = 115.56$, $p < 0.0001$. This indicates the presence of the MARC effect (Nuerk et al., 2004), that is, an advantage of the odd-left and even-right mapping over the odd-right and even-left mapping. The interaction between MARC compatibility and group did not yield a significant improvement of the model's fit, $\chi^2(2) = 4.03$, $p = 0.13$. SNARC compatibility significantly improved the fit when added to the model, $\chi^2(1) = 39.45$, $p < 0.0001$, but its interaction with group did not ($\chi^2(2) = 0$, $p = 1$). The resulting (final) model (AIC = 65279, BIC = 65361, Log-Likelihood = −32626) did not significantly differ from any of the alternative models which included the additional fixed factors entered in the magnitude comparison analysis (magnitude, distance), the interaction between these two factors, or interactions between either of these factor and SNARC compatibility, all $\chi^2 \leq 5.20$, all $ps \geq 0.07$.

REGRESSION ANALYSES

To further characterize the effects emerged in the mixed models analyses, we ran a series of regressions focused on the SNARC effect and on the distance effect.

SNARC effect

We first focused on the interaction between SNARC compatibility and group revealed by the mixed models analysis of the comparison RTs and by the corresponding lack of interaction in the parity RTs. For each patient, we computed an individual regression on the RT difference (dRT) between right and left effector responses using a binary predictor (0 for numbers smaller than the reference, 1 for numbers larger than the reference) for the comparison task[1] and a continuous predictor (1, 2, 3,...) for the parity task (see Gevers et al., 2006). We then performed one-tailed t-tests against zero on the regression slopes (Lorch and Myers, 1990), because the SNARC effect is indexed by a significant negative slope (Fias et al., 1996). The latter reveals an advantage of the left over the right effector (i.e., positive dRTs) for small numbers that reverses (i.e., negative dRTs) for large numbers (see **Figures 1** and **2**).

The regression analyses confirmed the presence of a SNARC effect in both tasks and in both groups (N+: $t(5) = -3.33$, $p < 0.05$ for comparison task and $t(5) = -2.26$, $p < 0.05$ for parity task; N−: $t(6) = -1.95$, $p < 0.05$ for comparison task and $t(6) = -2.75$, $p < 0.05$ for parity task). The direct comparison of the slopes of N+ and N− patients confirmed that the SNARC effect was significantly stronger (i.e., the slopes were more negative) for the

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[1] The use of a categorical rather than continuous magnitude predictor for the analysis of comparison dRTs has become a standard approach after Gevers et al.'s (2006) study. We also performed the same regressions with a continuous predictor and the results were virtually identical.

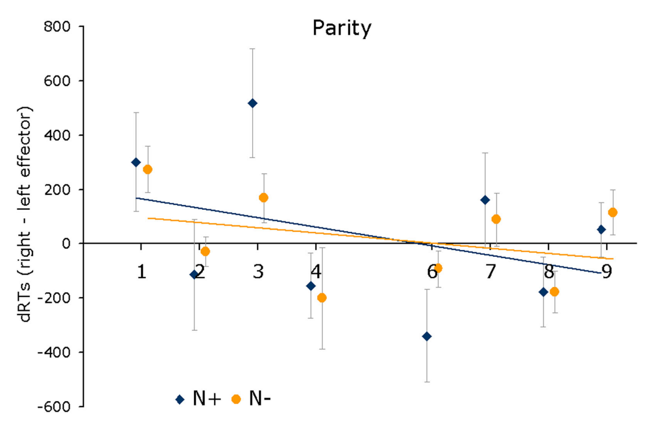

FIGURE 1 | Parity task. The mean difference in RT between right and left effector responses (dRT) to each number is plotted as a function of numerical magnitude, separately for N+ and N− groups. The lines represent the regression fits for each group, computed using a continuous magnitude predictor. Error bars represent ± SEM.

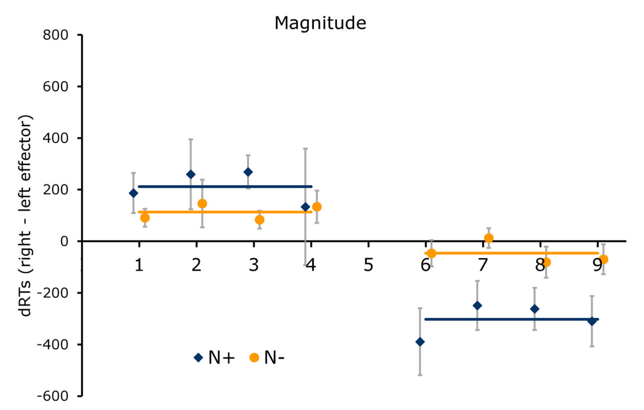

FIGURE 2 | Comparison task. The mean difference in RT between right and left effector responses (dRT) to each number is plotted as a function of numerical magnitude, separately for N+ and N− groups. The lines represent the regression fits for each group, computed using a categorical magnitude predictor. Error bars represent ± SEM.

neglect group in the comparison task ($t(11) = -2.12$, $p < 0.05$, one-tailed) but not in the parity task ($t(11) = -1.0$, $p = 0.34$, ns). Inspection of **Figure 2** suggests that the difference between N+ and N− in terms of SNARC effect for number comparison is more evident for large numbers than for small numbers. We therefore analyzed the difference between groups in terms of an interaction with magnitude. The ANOVA on dRTs with group (N+ vs. N−) and magnitude (small vs. large) as factors showed an interaction that just missed significance, $F(1,11) = 4.48$, $p = 0.058$. Follow-up t-tests revealed that the mean dRT for numbers 6–9 was significantly larger in N+ than in N− (−302 ms vs. −46 ms; $t(11) = -3.14$, $p < 0.05$, two tailed), whereas the mean dRTs for numbers 1–4 did not differ (N+: 212 ms; N−: 114 ms; $t(11) = 0.92$, $p = 0.38$, ns)[2]. Note that there was no hint of a difference between groups in the parity task even when separating small and large numbers (1–4: $t(11) = 1.1$, $p = 0.29$; 6–9: $t(11) = 1.26$, $p = 0.23$). In summary, the SNARC effect was present in both groups and in both tasks. In the comparison task only, neglect patients showed a stronger SNARC effect than patients without neglect, particularly for numbers larger than the reference (i.e., 6–9).

MARC effect

To further investigate the effect of MARC compatibility in the parity task (also see **Figure 1**), we re-run the individual regression analyses on dRTs introducing a parity predictor (binary coded as 0 for odd and 1 for even) in addition to the magnitude predictor. In this way we simultaneously assessed the effect of MARC (parity predictor) and SNARC (magnitude predictor) on the dRTs within a single multiple regression. As for the SNARC, the MARC effect is indexed by negative regression weights (i.e., smaller dRTs for even than for odd numbers) and it can be statistically assessed by a one-tailed *t*-test against zero. As expected, in the parity task both SNARC and MARC were significant (magnitude predictor: $t(12) = -3.29$, $p < 0.01$; parity predictor: $t(12) = -2.43$, $p < 0.05$), whereas in the comparison task only the SNARC effect was significant (magnitude predictor: $t(12) = -3.4$, $p < 0.01$; parity predictor: $t(12) = -0.27$, $p = 0.79$). The MARC regression weights in the parity task did not significantly differ between neglect and control patients ($t(11) = 0.54$, $p = 0.6$, two tailed).

Distance effect

To further investigate the interaction between magnitude, distance, and group revealed by the mixed models analysis of the comparison data, we computed for each patient two regressions on the RTs using numerical distance (from 1 to 4) as predictor, separately for numbers smaller vs. larger than the reference. We reasoned that an asymmetric distance effect should be indexed by a significant difference between slopes for numbers 1–4 vs. numbers 6–9. This was indeed the case for N+ ($t(5) = 2.76$, $p < 0.05$, two tailed) but not for N− ($t(6) = 1.55$, $p = 0.17$). We then assessed whether the asymmetry could be localized to the number immediately preceding the reference (that is, 4; see **Figure 3**), as reported by Vuilleumier et al.'s, 2004; also Salillas et al., 2009). A *t*-test between the RTs to 4 (mean = 1363 ms) and 6 (mean = 1160ms) was significant in N+ ($t(5) = 3.2$, $p < .05$, two tailed) but not in N− ($t(6) = 0.92$, $p = 0.39$, ns). As can be noted in **Figure 3**, this pattern was mirrored by the error rates (N+: 10.1% for 4 vs. 4.4% for 6; N−: 5.3% for 4 and 5.3% for 6). Notably, RTs to 4 and 6 in the N+ group did not differ in the parity task ($t(5) = -1.28$, $p = 0.26$, ns).

To compare the asymmetry of the distance effect across groups, we computed regression slopes using only the two numbers immediately smaller (3 and 4) and the two numbers immediately larger (6 and 7) than the reference. We then subtracted the slopes for

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[2] Note that the three-way interaction between SNARC compatibility, magnitude and group was not significant in the mixed models analysis. This discrepancy might reflect a higher sensitivity of the dRT analysis, which is specifically designed to investigate the SNARC effect (i.e., other effects that strongly modulate RTs are canceled out by the subtraction).

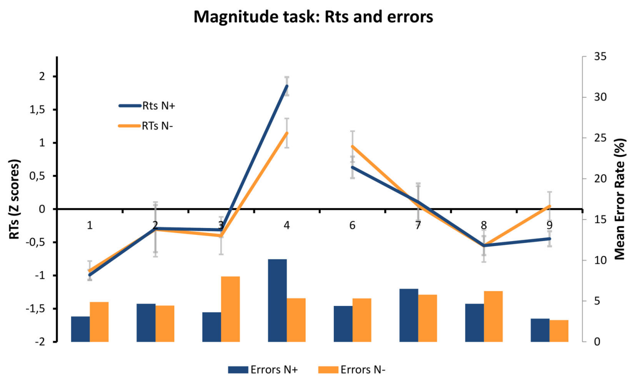

FIGURE 3 | Distance effect in the comparison task. Mean RTs (normalized to z-scores for better visualization) and error rates (percentages) are plotted as a function of numerical distance, separately for N+ and N−. Error bars represent ± SEM.

large numbers from the slopes for small numbers (note that distance slopes are negative) to obtain an index that quantifies the asymmetry of the distance effect, henceforth Distance Asymmetry Index (DAI). Perfect symmetry is indexed by a value of 0, stronger distance effect for small than for large numbers is indexed by a negative value, and stronger distance effect for large than for small numbers is indexed by a positive value. The DAI was negative and significantly different from zero for N+ (DAI = −243; $t(5) = -5$, $p < 0.01$, two tailed) but not for N−, (DAI = −64.7; $t(6) = -1.12$, $p = 0.31$, ns). Moreover, a direct comparison between the two groups showed that the DAI was larger for N+ than for N− ($t(11) = -2.32$, $p < 0.05$, two tailed).

CORRELATIONS WITH NEGLECT SEVERITY

Finally, we explored whether the atypical pattern observed in N+ for both SNARC and distance effects correlated with the overall index of neglect severity, that is the BIT score. The correlations were computed across the entire sample of right brain damaged patients, that is, regardless of their classification as N+ or N−. Correlations should be treated with caution due to the small sample size and are reported only for the sake of completeness. The BIT score was positively correlated with the individual regression weights of the comparison SNARC effect ($r = 0.64$, $p < 0.05$). The correlation between BIT score and DAI just missed significance ($r = 0.53$, $p = 0.065$). We also assessed the correlations between BIT score and the two effects modulating performance in the parity task, that is SNARC and MARC, indexed by the individual regression weights. Both correlations did not reach significance (SNARC: $r = 0.35$, $p = 0.24$; MARC: $r = 0.436$, $p = 0.136$).

GENERAL DISCUSSION

Our results supported the hypothesis that the effect of spatial neglect on number processing is modulated by task demands. When the task did not require explicit processing of numerical magnitude, as in parity judgments, the performance of neglect patients was indistinguishable from that of control patients without neglect. Indeed, group failed to interact with any of the numerical factors introduced in the mixed model, including SNARC compatibility. Moreover, direct assessment of the SNARC effect using the regression approach on dRTs showed a classic negative slope for neglect patients, thereby indexing implicit access to numerical magnitude, but the slope did not differ from that of control patients. These results replicate and extend the findings of Priftis et al. (2006), who found no difference between neglect patients and healthy controls.

In contrast, neglect patients' performance was markedly different from that of control patients when explicit access to numerical magnitude was part of the task demands. The effect of neglect on number comparison was indexed by two distinct phenomena: (i) a stronger SNARC effect, particularly for numbers larger than (i.e., to the right of) the reference, and (ii) an asymmetric distance effect, caused by slowing of the number immediately smaller than (i.e., to the left of) the reference number (as in Vuilleumier et al., 2004). These two findings, as well as their theoretical implications, are discussed below. It is important to reiterate that the number comparison task (unlike the number bisection task used by Priftis et al., 2006) was identical to the parity judgment task both in terms of stimuli (i.e., a single digit presented at fixation) and response requirements (i.e., key-press responses using the index and middle fingers of the right hand). Both tasks also required to switch the response-key assignment between blocks of trials. Thus, any difference in performance between the two tasks must be attributed to how stimulus information is internally processed to accomplish the task. Moreover, since both groups of participants had right hemisphere lesions (and lesion site was quite heterogeneous across patients; see **Table 1**), any difference that emerged between tasks in neglect patients must be attributed to their failure in orienting to or exploring the contralesional portion of number space due to impaired attentional mechanisms. The manipulation of the task whilst keeping constant the stimuli allows one to establish that the differences between the two groups are due to the aspect under investigation (Bonato et al., 2012, for discussion).

Our findings on the comparison SNARC effect suggest that, after processing a large number, the difference in speed between responses in contralesional (relative left) space and ipsilesional (relative right) space is unusually large for neglect patients with respect to patients without neglect. Assuming that processing a large number entails a rightward shift of attention, the exaggerated effect of number-space compatibility after ipsilesional (i.e., rightward) orienting seems to resemble the marked difficulty of neglect patients in "disengaging" from an ispilesional (i.e., right) location where attention has been directed (Posner et al., 1984). This bias, known as the "disengage deficit," is consistently found in neglect patients following both stimulus-driven orienting to peripheral cues (Losier and Klein, 2001) and reflexive orienting following central symbolic cues (Bonato et al., 2009). Thus, we propose that the stronger SNARC effect for large numbers observed in neglect patients in comparison to control patients might be an instance of the ipsilesional hyper-attention and/or contralesional impaired orienting that, in physical space, manifests itself as a disengage deficit. That is, neglect patients would have a difficulty to disengage from larger magnitudes (right on the mental number line) to respond in the left (physical) space. Interestingly, the index of neglect severity (BIT score) correlated with the size of the SNARC effect across the entire sample of right brain damaged patients, suggesting again a parallel with the visuospatial domain, where Bonato et al. (2009) found that the same index correlated with the size of the disengage deficit. A modulation of the SNARC effect during number comparison, but not during parity judgments, was also observed by Rusconi et al. (2011) in healthy participants when rTMS was delivered to the frontal regions that support attention orienting. Most notably, TMS over the right frontal eye fields (FEF) in healthy participants decreased the comparison SNARC effect for small numbers. The finding that FEF has a key role for orienting in number space fits well with the hypothesis that attentional orienting in parietal spatial maps is driven by eye movement programming (i.e., premotor theory of attention; Casarotti et al., 2012).

The result that the SNARC effect is modulated by neglect has important theoretical implications. Our findings fit well with the assumption that numbers are spatially coded and that the SNARC effect taps their spatial correspondence with the position of response. However, the visuospatial origin of the SNARC effect is strongly disputed (Gevers et al., 2006, 2010; Proctor and Cho, 2006; Santens and Gevers, 2008). A computational model of the SNARC effect (Gevers et al., 2006) dispenses with the spatial coding of numbers and assumes that left and right response codes are activated by a verbal-conceptual coding of numbers as small and large, respectively (Fias et al., 2011, for review). This association can also be cast within the broader theoretical framework of polarity matching (Proctor and Cho, 2006), where binary choice tasks induce polarity coding (+ vs. −) of stimuli and responses. Thus, the SNARC effect would be the result of coding large numbers as [+] and small numbers as [−], which would then produce match or mismatch with the coding of responses as [+] for right and [−] for left. However, if the SNARC effect were merely an instance of polarity correspondence, neglect should not have any effect on it, or at least it should exert identical effects on the parity and the comparison tasks. Of course the notion of implicit vs. explicit processing may be invoked by any theory of the SNARC effect to explain the fact that neglect affected only the comparison task, but what still needs to be explained is *why* the comparison SNARC effect is affected by neglect. In this regards, it is difficult to envisage how a deficit of visuospatial attention (i.e., neglect) would influence the SNARC effect if number–space interactions do not involve a visuospatial code, as posited by verbal–conceptual accounts. One could still argue that neglect may affect the verbal–conceptual association between numbers and space. If so, this should hold for another type of number–space association that has a firm verbal–conceptual basis, that is the association between parity status and response space (MARC effect; Nuerk et al., 2004; Iversen et al., 2006). This issue was not investigated in the study of Priftis et al. (2006); in the present study, we found that the MARC effect in the parity task was not modulated by neglect, even though number parity was the task-relevant dimension and had to be explicitly processed. This rules out the hypothesis that the effect of neglect emerges only on the task-relevant dimension irrespectively of the nature of the task. Taken together, our findings are inconsistent with a purely verbal–conceptual account of number–space interactions. More generally, any explicit account of the effect of neglect on number processing requires – as a minimum – that visuospatial representations substantially contribute in shaping the number–space interaction, as in the computational model of Chen and Verguts (2010).

Our findings are also consistent with the recent proposal that numbers might be associated with multiple spatial codes, and that, depending on the task, these codes have a verbal or visuospatial basis (van Dijck et al., 2009; Gevers et al., 2010). Van Dijck and colleagues investigated the effect of working memory load on the SNARC effect. They found that the SNARC effect in parity judgments disappeared under verbal load but not under spatial load, whereas the opposite was found for the SNARC effect in number comparison (also see Herrera et al., 2008). Further evidence for the co-existence of verbal–spatial and visuospatial coding of numbers was provided by Gevers et al. (2010), although they concluded that the former is the dominant one. A dual-coding account of our findings would suggest that the SNARC effect in number comparison is primarily driven by the visuospatial coding of numbers (Herrera et al., 2008; van Dijck et al., 2009), which in turn is affected by neglect, whereas the SNARC effect in parity judgment is primarily driven by the verbal–spatial code, which is not affected by neglect. Note that this alternative account does not necessarily require the distinction between explicit and implicit processing. Nevertheless, our results are still inconsistent with the claim that verbal–spatial coding is predominant across tasks (Gevers et al., 2010) and that the SNARC effect does not imply a visuospatial coding of numbers (Gevers et al., 2006; Proctor and Cho, 2006; Santens and Gevers, 2008; Fias et al., 2011).

While the modulation of the comparison SNARC effect shows that neglect affects the interaction between numbers and physical space (i.e., upon spatially organized responses), the asymmetric distance effect is complementary (and orthogonal) to the latter, because it shows that neglect can affect number processing *per se*, regardless of the spatial characterization of the responses (i.e., irrespectively of response side). Both effects, however, can be observed only when magnitudes must be explicitly manipulated on the mental number line. The asymmetry of the distance effect was largely due to the slowing of the number immediately smaller than (i.e., to the left of) the reference number; importantly, our asymmetry index (DAI) allowed us to characterize this effect in relative (rather than absolute) terms and to establish that this contralesional bias specifically affects neglect patients. Crucially, as predicted by the explicit vs. implicit processing account (Priftis et al., 2006), response speed to the same number (4) was unaffected by neglect in the parity task. Therefore, our results replicate and extend those of Vuilleumier et al. (2004) and Salillas et al. (2009). We suggest that the asymmetric distance effect indexes a difficulty of contralesional orienting in the number space. That is, we assume that numbers are flexibly coded as left or right with respect to the reference number (also see Vuilleumier et al., 2004) and that spatial attention is shifted (leftward or rightward) from this anchor point to the spatial position of the target number on the mental number line. The apparent selectivity of the bias for the number immediately to the left of the reference might be a consequence of the interaction with the distance effect, which makes that number more difficult to process than any other number on the same side of the number line. An ERP signature of the orienting bias in the number space was reported by Priftis et al. (2008) using a numerical oddball task. With respect to right hemisphere damaged controls without neglect, neglect patients had slower P3b brain waves (see Lhermitte et al., 1985, for comparable results with visuospatial stimuli) in response to a small target number ("one," which is to the left of the non-target "five"), but faster brain waves in response to a large target number ("nine," which is to the right of "five"). This pattern resembles that of neglect patients in allocating visuospatial attention in the physical space (Làdavas et al., 1990).

The orienting bias in the number space is theoretically important because it is inconsistent with the recent proposal that a position-specific deficit to initial items in verbal working memory (Fias et al., 2011; van Dijck et al., 2011) could explain the biases in numerical processing that were originally attributed to spatial neglect (Zorzi et al., 2002). The verbal working memory account was developed in the context of a single case study to explain the patient's rightward bias in number interval bisection as due to a difficulty to efficiently keep in mind the initial numbers of the to-be-bisected interval, but it has also been proposed as a general and alternative account of the (putative) effect of neglect on number processing. In this regard, the verbal working memory account falls short in explaining the pattern observed in our number comparison task, where the only number that must be kept in working memory is the reference (note that the same applies to the numerical oddball task of Priftis et al., 2008), and more generally it cannot explain the dissociation between explicit and implicit processing of numerical magnitude. Moreover, its prediction that the interval bisection bias should be identical for any kind of ordered information is challenged by the dissociations observed in neglect patients by Zorzi et al., 2006; also see Zamarian et al., 2007) between numerical and non-numerical ordered sequences (i.e., intervals formed by numbers, letters, or months). Note also that the cortical overlap in the human intraparietal sulcus for the processing of numerical and non-numerical order revealed by fMRI (Fias et al., 2007) can be resolved into distinct clusters of activation using multivariate classifiers (Zorzi et al., 2011). Finally, Priftis et al. (2012) recently showed that optokinetic stimulation – a technique inducing visuospatial attention shifts by means of activation of the optokinetic nystagmus – modulated the number bisection bias in one neglect patient, thereby demonstrating that the rightward bias had an attentional origin.

While the studies on neglect patients clearly show that a deficit of visuospatial attention can affect number processing, there is also mounting evidence that experimental manipulations of the deployment of visuospatial attention in healthy participants affects performance in numerical tasks. For example, Göbel et al. (2006) induced neglect-like performance in number interval bisection by applying rTMS on the right parietal lobe of healthy participants. Notably, the stimulation site was functionally (and individually) defined such that TMS interfered with visuospatial attention (i.e., visual search task). Stoianov et al. (2008) demonstrated that task-irrelevant lateralized visuospatial cues, which are known to induce stimulus-driven orienting of attention, can modulate performance in both number comparison and parity judgment. Even though responses were verbal and non-spatial, left cues interfered with the processing of large numbers, whereas right cues interfered with small numbers (also see Kramer et al., 2011). Consistent results were found by Nicholls and McIlroy (2010) using the number interval bisection task. Finally, Loetscher et al. (2008) observed response biases in random number generation that were congruent with the direction of lateral head turns (leftward or rightward), which are known to reallocate visuospatial attention. Together, the findings on neglect patients and healthy participants across a variety of different methods converge in supporting the hypothesis that the spatial aspects of numerical processing are not epiphenomenal and that spatial attention is routinely involved in number processing tasks.

In conclusion, the hypothesis that the manipulation of numerical magnitudes entails shifts of attention on a spatially oriented mental number line remains the most viable explanation for the intriguing phenomenon of number space neglect and, more generally, for the interactions between numbers and space. The effect of neglect on the explicit processing of numerical magnitude can be understood in terms of both a failure to orient to smaller (i.e., contralesional) magnitudes and a difficulty to disengage from larger (i.e., ipsilesional) magnitudes on the number line, which resembles the disrupted pattern of attention orienting in visual space. Though many details still need to be worked out, this conclusion is consistent with the idea that cortical circuits originally subserving spatial cognition and attention are "recycled" for mathematical learning (Dehaene and Cohen, 2007). It also fits well with the idea that componential, dynamic sensorimotor simulations underlie the representation of concepts (Barsalou, 1999), as also shown by the remarkable flexibility of spatial coding for numbers as a function of context. Notwithstanding the dissociations between number space and physical space, which are rather unsurprising given the complex and multi-faceted nature of hemispatial neglect, the "strong" (i.e., homeomorphic) number line hypothesis has still a long way to go.

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Automatic and intentional number processing both rely on intact right parietal cortex: a combined fMRI and neuronavigated TMS study

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Practice and training usually lead to performance increase in a given task. In addition, a shift from intentional toward more automatic processing mechanisms is often observed. It is currently debated whether automatic and intentional processing is subserved by the same or by different mechanism(s), and whether the same or different regions in the brain are recruited. Previous correlational evidence provided by behavioral, neuroimaging, modeling, and neuropsychological studies addressing this question yielded conflicting results. Here we used transcranial magnetic stimulation (TMS) to compare the causal influence of disrupting either left or right parietal cortex during automatic and intentional numerical processing, as reflected by the size congruity effect and the numerical distance effect, respectively. We found a functional hemispheric asymmetry within parietal cortex with only the TMS-induced right parietal disruption impairing both automatic and intentional numerical processing. In contrast, disrupting the left parietal lobe with TMS, or applying sham stimulation, did not affect performance during automatic or intentional numerical processing. The current results provide causal evidence for the functional relevance of right, but not left, parietal cortex for intentional, and automatic numerical processing, implying that at least within the parietal cortices, automatic, and intentional numerical processing rely on the same underlying hemispheric lateralization.

Keywords: automaticity, congruity effect, distance effect, intentional processing, lateralization, numerical cognition, parietal lobe, brain stimulation

INTRODUCTION

Extensive practice of a new perceptual, cognitive, or manual skill usually leads to faster processing speed, higher accuracy, and eventually to automatic processing of the practiced material (Logan, 1988; Vanlehn, 1996; Rickard, 1997). For example, during development, children show a increased processing speed and lower accuracy during numerical quantity processing (Sekular and Mierkiewicz, 1977; Girelli et al., 2000; Rubinsten et al., 2002). At the same time, practice leads to an increased interference of the numerical value of a presented digit when children are required to ignore its numerical value during the performance of another task, such as physical size comparison (Girelli et al., 2000; Rubinsten et al., 2002). Similarly, after extensive training with new numerical symbols, adult participants become faster, more accurate with intentional processing of these numerical symbols, and more automatic at processing the newly acquired numerical values (Tzelgov et al., 2000; Cohen Kadosh et al., 2010).

Previous studies have suggested that intentional and automatic processing are only quantitatively different, and stem from the same underlying mechanism (Tzelgov and Ganor-Stern, 2005; Cohen Kadosh and Walsh, 2009; Reis et al., 2009). Others have suggested that intentional and automatic processing are qualitatively different and stem from different mechanisms (Logan, 1985; Lewis and Miall, 2003; Rossetti et al., 2003; Bugden and Ansari, 2011). This dispute is important not only for our understanding of the relationship between automatic and intentional processes. It has also theoretical implications for several other domains, such as neuropsychological studies and rehabilitation (Reis et al., 2009; Rubinsten and Henik, 2009), as well as for cognitive and neuroimaging studies which prefer using automatic processing, rather than intentional processing, to infer about the mental representation of a cognitive or perceptual entity independent of subject's strategies (Barsalou, 1999; Tzelgov and Ganor-Stern, 2005; Cohen Kadosh and Walsh, 2009).

In the field of numerical cognition, automatic numerical processing can be assessed by the numerical Stroop task (or as referred to by others, the size congruity task) and intentional processing can be assessed by a numerical comparison task (Tzelgov and Ganor-Stern, 2005).

In the numerical Stroop paradigm, subjects are presented with two numerical stimuli on a computer screen and required to compare these stimuli according to their physical size. The stimuli can be incongruent (the physically larger digit is numerically smaller, e.g., 2 4), neutral (the stimuli differ only in the relevant dimension, e.g., 2 2), or congruent (the physically larger digit is also numerically larger, e.g., 2 4). Even when instructed to ignore the numerical value, healthy adult subjects show a strong congruity effect (longer reaction times for incongruent trials compared to congruent trials) because the numerical value is processed automatically. This congruity effect, which is termed *size congruity effect*, has been considered for almost 20 years as a marker of automatic numerical processing (Henik and Tzelgov, 1982; Tzelgov et al., 1992; Schwarz and Heinze, 1998; Schwarz and Ischebeck, 2003; Szucs et al., 2007; Cohen Kadosh et al., 2008b, 2011; Van Opstal et al., 2008b; Gebuis et al., 2009; Rubinsten and Henik, 2009; Santens and Verguts, 2011). It has been shown that those who have better numerical abilities exhibit a greater level of automaticity as reflected by a *larger* size congruity effect (Girelli et al., 2000; Rubinsten et al., 2002; Rubinsten and Henik, 2005, 2006; Cohen Kadosh et al., 2007b; Mussolin and Noël, 2008).

In a numerical comparison task, which assesses intentional numerical processing (Tzelgov and Ganor-Stern, 2005), subjects are asked to attend to the numerical dimension and to compare stimuli according to their numerical value. One of the most used effects to assess the efficiency of intentional numerical processing is the *numerical distance effect* (Moyer and Landauer, 1967). As the name implies, the difference in numerical value influences the time needed to compare stimuli; the larger the numerical distance (e.g., 2–8 vs. 2–3), the easier it is to decide which of the numbers has the greater (or smaller) numerical value, as indicated by a shorter reaction time (RT) for pairs with a larger numerical distance. It has been shown that the better the numerical abilities are, the *smaller* the numerical distance effect (Sekular and Mierkiewicz, 1977; Price et al., 2007; Holloway and Ansari, 2009; Mussolin et al., 2010; Bugden and Ansari, 2011). However, it must be noted that a smaller numerical distance effect does not indicate necessarily better numerical abilities. For example, the numerical distance effect can be smaller due to *slower* processing time of the larger distance, which clearly reflects an impairment in the intentional processing of numerical information (for a review see Sandrini and Rusconi, 2009).

The current knowledge in the field of numerical cognition does not allow us to settle on whether automatic and intentional processing are parts of the same mechanism or not. Previous behavioral, neuroimaging, modeling, and neuropsychological studies have yielded mixed results. For example, a recent behavioral study has shown that intentional processing of numerical information is correlated with mathematical achievement scores, while no such correlation has been obtained for automatic numerical processing (Bugden and Ansari, 2011). In contrast, others have found that highly automatic numerical processing is associated with intact intentional numerical processing such as mathematical abilities, while impaired automatic numerical processing is associated with low mathematical abilities (i.e., developmental dyscalculia; Rubinsten and Henik, 2009). Similarly, some neuroimaging studies have suggested that different brain areas are associated with intentional vs. automatic numerical processing (Kaufmann et al., 2005; Tang et al., 2006), while others have challenged these findings (Schwarz and Heinze, 1998; Szucs et al., 2007). Furthermore, one of the assumptions of a recent computational model is that the size congruity effect, which signals automatic numerical processing, and the numerical distance effect, related to intentional numerical processing, originate from different mechanisms (Santens and Verguts, 2011), see also (Cohen Kadosh et al., 2008a; Van Opstal et al., 2008a). In contrast, another work has suggested that both effects stem from the same source (Schwarz and Ischebeck, 2003). However, all the aforementioned studies have examined the relationship between brain and behavior in a correlative fashion, and hence do not allow for causal inference.

In the current study, we used transcranial magnetic stimulation (TMS), a non-invasive brain stimulation method, to examine and compare the causal relationship between automatic and intentional numerical processing and the parietal lobes. At the brain level, the intraparietal sulcus (IPS), a brain structure in the parietal lobe, has been shown to be involved in numerical representation in a variety of tasks (for meta-analyses see Cohen Kadosh et al., 2008c; Arsalidou and Taylor, 2011)). In a previous study we have shown that after stimulation to the right IPS, participants showed impairment in automatic processing of numbers, as reflected by a reduced size congruity effect. In contrast, stimulation of the left IPS, or sham stimulation did not affect automatic numerical processing (Cohen Kadosh et al., 2007b). In the current study we used the data that we reported at Cohen Kadosh et al. (2007b) to examine whether this observed impairment in automatic numerical processing will be associated with impairment in intentional numerical processing, as reflected by the numerical distance effect. The predictions are clear: if the same parietal functional asymmetry underlies both automatic and intentional numerical processing, disruption of right IPS, but not left IPS or sham stimulation, will affect both the size congruity effect and the numerical distance effect. Contrarily, if automatic and intentional numerical processing are subserved by a different or no parietal functional asymmetry, a dissociation between the two processes and/or the stimulation sites can be expected. For example, right IPS stimulation could only impair automatic numerical processing as shown previously but not intentional numerical processing, while left IPS stimulation could only impair intentional numerical processing but not automatic numerical processing (double dissociation). Alternatively, both left and right IPS stimulation could impair intentional numerical processing but only right IPS stimulation would impair automatic numerical processing (single dissociation). Any of such result patterns would therefore indicate different brain mechanisms underlying intentional and automatic numerical processing.

MATERIALS AND METHODS

DETERMINATION OF OPTIMAL SAMPLE SIZE

The current study is a conceptual follow-up of our previous work on automatic number processing where we used the identical numerical Stroop task and applied TMS to disrupt left or right IPS activation to induce dyscalculia-like behavior in healthy volunteers (Cohen Kadosh et al., 2007b). In a methodological follow-up, we then (i) quantified the exact behavioral effects induced by TMS using different coil positioning approaches, (ii) calculated the standardized experimental effect sizes, and (iii) conducted a statistical power analysis in order to determine the optimal sample size required to reveal statistical significance. These power analyses revealed that when using fMRI-guided TMS neuronavigation, five participants are sufficient to reveal the revealed, or any greater, behavioral effect of parietal TMS on automatic numerical processing as statistically significant (Sack et al., 2009). In the current study, we now aimed to examine whether this observed impairment in automatic numerical processing is also associated with impairment in intentional numerical processing, as reflected by the numerical distance effect. In the context of the current research question, we determined the optimal sample size based on our previous studies (Cohen Kadosh et al., 2007b; Sack et al., 2009) using the following procedure and parameters: first, alpha was conventionally defined to be statistically at an α-error-probability of 5% and beta to be at an β-error-probability of 20%, resulting in a test power of (1-beta) = 80%. The expected experimental effect size was estimated based on the effect size on the SCE as revealed in Sack et al., 2009; where fMRI-guided TMS over PPC resulted in an effect size of Cohen's $d = 1.13$ for the difference in SCE between sham and TMS; and of $f^2 = 1.23$ for the interaction between TMS and congruency as shown by the two-way repeated measures analysis of variance (ANOVA) with TMS (sham or TMS) and congruency (incongruent, neutral, or congruent) as within-subject factors. The significance level (α), the test power (1-β), the experimental effect (Cohen's d or f^2), and the optimal sample size (opt n) are interdependent, and thus, after determining any three of these parameters, it is possible to calculate the fourth. Using the aforementioned procedure and parameters, we calculated an optimal sample size of $n = 5$ for our current study, now aiming to reveal whether under these conditions, fMRI-guided TMS over PPC would likewise statistically impair intentional numerical processing based on the same sample size.

Note that using a small sample size may lead to underpowered analyses, thus the likelihood of making a type I error is the primary concern. However, as the results below indicate, this has not been the case as the highest order interaction has been observed.

Participants

Five participants (four males, mean age = 28.6 years, SD = 4.5), with normal or corrected-to-normal vision and no history of neurological or psychiatric disorders, participated in this study and gave their inform consent. None of the participants had taken part in a TMS experiment before. Ethical approval was given by the local medical ethical committee in Maastricht University, The Netherlands. All the participants were recruited from an academic environment.

Stimuli and paradigm

The participants were asked to decide which of two visually presented digits had a larger physical size or numerical value. These conditions were presented in separate blocks. The stimuli, 0.8° or 1.1° vertical visual angles in size, appeared at the center of a screen, and were separated center-to-center by 4° horizontal visual angles. In the small numerical distance condition the numerical difference between the two digits was one unit (the pairs 1–2, 3–4, and 8–9). In the large numerical distance condition the numerical difference between the two digits was six units (the pairs 1–7, 2–8, and 3–9).

Each trial began with an asterisk as a fixation point, presented for 500 ms at the center of a computer screen. Five hundred millisecond after the fixation point disappeared, a pair of visual digits appeared for 1 s. The inter-trial interval was 6 s, and the inter-block interval was at least 15 s.

PROCEDURE

Participants were instructed to decide which one of two digit stimuli in a given display was either physically or numerically larger (**Figure 1**). They had to indicate their choice by pressing the key corresponding to the side of the display with the selected digit (right hand if the right stimulus was larger, and left hand if the left stimulus was larger). Participants were encouraged to respond as quickly as possible while avoiding mistakes, and to attend only to the relevant dimension in each task (i.e., physical or numerical size). Presentation software (Neurobehavioral Systems, San Francisco, CA, USA) was used to present the stimuli and record the speed and accuracy of the behavioral responses. The experiment was preceded by a training session.

TMS experiment

Each volunteer underwent four TMS sessions spread over two different days. The order of numerical and physical blocks was counterbalanced in an ABBA design for three participants and in a BAAB design for the rest. The order of real and sham stimulation to the left IPS and right IPS (four sessions) was also counterbalanced. On each day two sessions took place. Per day, participants received real TMS to one hemisphere and sham TMS to the other hemisphere. The stimulation order for the fifth participant was randomly chosen. Participants underwent event-related triple-pulse TMS while comparing two-digits with regards to either numerical value or physical size. Triple-pulse TMS (Medtronic Functional Diagnostics A/S, Skovlunde, Denmark; maximum stimulator output, 2 T) was applied at 220, 320, and 420 ms after stimulus onset

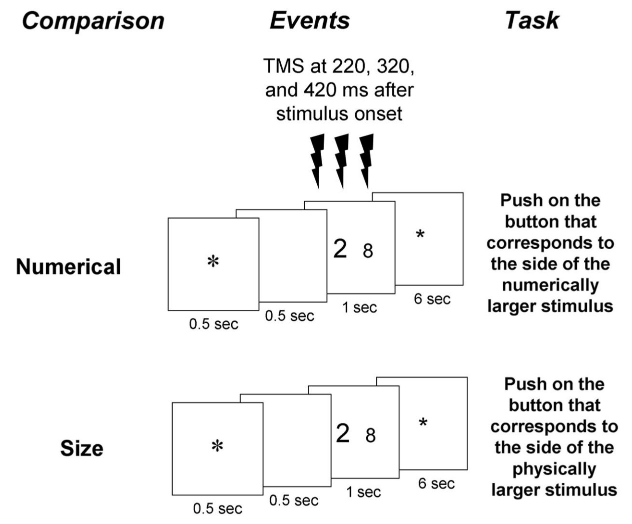

FIGURE 1 | Experimental paradigm. Two tasks were presented in separate blocks: a physical size comparison task and a numerical comparison task. The numerical values appeared in these tasks can affect automatic and intentional numerical processing, respectively. Each pair of stimuli was preceded by a fixation point and a blank of 500 ms each, and remained visible for 1 s. After an inter-trial interval of 6 s a new trial began with the presentation of a fixation point. Responses were indicated by a button press on the side corresponding to the larger relevant dimension. Triple-pulse TMS at 60% of the maximum stimulator output was applied at 220, 320, and 420 ms after stimulus onset.

at 60% of maximum stimulator output. We chose the timing of the pulses based on previous ERP studies that found modulation of the different ERP components by the numerical distance and size congruity (e.g., Cohen Kadosh et al., 2007a; Libertus et al., 2007; Szucs et al., 2007).

Small and large numerical distances were randomly sampled with an equal sampling for each condition. A total of 576 trials were presented to each participant [36 trials × 4 sessions (right TMS, left TMS, right sham, left sham) × 2 numerical distances (small, large) × 2 tasks (physical/numerical), for the numerical distance effect analysis; 24 trials × 4 sessions (right TMS, left TMS, right sham, left sham) × 3 congruity (congruent, neutral, incongruent) × 2 tasks (physical/numerical), for the size congruity effect analysis]. Correct responses had to be made equally often with the left and right hand. Please note that the analysis of the numerical distance effect and congruity effect has been made based on the same behavioral data. That is based on for calculating the congruity effect we included the congruity conditions (across numerical distances), and for the numerical distance effect we included the different numerical distance conditions (across congruity conditions).

Mean RTs for each participant in each condition were calculated for correct trials only. RTs that were 2.5 SDs from the mean of each condition for each individual were excluded (less than 2%).

fMRI localizer

The exact TMS target site within left and right IPS was determined individually using an fMRI localizer session (Cohen Kadosh et al., 2007b). Hence, prior to the TMS study, each participant underwent an fMRI session consisting of three runs, with each run being composed of eight blocks of numerical comparisons and eight blocks of physical size comparisons. Whole brain fMRI data were acquired with a Siemens 3 T scanner ("Allegra," Siemens, Erlangen, Germany). Functional images were acquired using a gradient-echo echo planar imaging sequence (16 axial slices; repetition time/echo time = 2500/30 ms; flip angle = 90°, field of view = 192 mm × 192 mm, voxel size: 3 mm × 3 mm × 5 mm). Stimulus presentation was synchronized with the fMRI sequence at the beginning of each trial. Each scanning session included the acquisition of a high-resolution T1-weighted 3-D volume using MPRAGE sequence (echo time 4 ms, 256 × 256 × 192 matrix, voxel dimensions = 1 mm × 1 mm × 1 mm) for co-registration and anatomical localization of functional data. Data were preprocessed and analyzed using the BrainVoyager QX 1.4 software package (BrainInnovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to allow for T1 equilibration. The remaining functional data sets were co-registered to Talairach-transformed anatomical data (Talairach and Tournoux, 1988) and 3-D motion-corrected for each participant. The 3-D functional data set was re-sampled to a voxel size of 3 mm × 3 mm × 3 mm. Further preprocessing included spatial smoothing with a Gaussian kernel (full-width at half-maximum = 8 mm, for the group analysis, and 3 mm for the individual analysis), linear trend removal, temporal high pass filtering (high pass: 0.00647 Hz), and autocorrelation removal. The predictor time courses (box-car functions) were convolved with a gamma distribution to account for the shape and delay of the hemodynamic response (Boynton et al., 1996).

The main purpose of these fMRI measurements was to individually map the exact activation network underlying the comparison tasks (Cohen Kadosh et al., 2007b), and to localize the individual activation hot spot underlying the size congruity and numerical distance effect using frameless stereotaxic TMS Neuronavigation (BrainVoyager TMS Neuronavigator).

fMRI-guided TMS neuronavigation

By superimposing the functional data on the anatomical reconstruction of the brain, the TMS coil can be neuronavigated to a specific anatomical and/or functional activation area of every participant, thus increasing the statistical power by optimizing the functional accuracy of TMS and significantly reducing the number of subjects needed to obtain statistical significance of a given effect size, as recently quantified using power analysis on different TMS localization approaches (Sack et al., 2009).

Individual imaging-guided TMS neuronavigation was performed using BrainVoyager TMS Neuronavigator. This system consists of several miniature ultrasound transmitters which are attached to the participant's head as well as to the TMS coil. These ultrasound markers continuously transmit ultrasonic pulses to a receiving sensor device. The measurement of the relative spatial position of these transmitters in 3-D space is based on the travel time of the transmitted ultrasonic pulses to three microphones built into the receiving sensor. In the next step, local spatial coordinate systems are created by linking the relative raw spatial position of the ultrasound senders to a set of fixed additional landmarks on the participant's head. The specification of these fixed landmarks is achieved via a digitizing pen that also hosts two transmitting ultrasound markers in order to measure its relative position in 3-D space. The nasion and the two incisurae intertragicae were used as the three anatomical landmarks in order to define the local coordinate system. After this stage, the system provides topographic information of the head ultrasound transmitters relative to a participant-based coordinate frame. Similarly, the TMS coil also hosts a set of ultrasound transmitters whose relative spatial positions are linked to fixed landmarks specified on the coil in order to calculate another local coordinate system. Once the local spatial coordinate system is defined for the participant's head and the TMS coil in real 3-D space, these coordinate systems have to be co-registered with the coordinate system of the MR space. For TMS–fMRI co-registration, the same digitized landmarks on the participant's head are specified on the head representation (mesh) of the participant in the fMRI software. Hence, using the BrainVoyager software, the anatomical landmarks were identified in the MRI scan of the participant's head and co-registered with the coordinates from the digitizer. After the landmarks specified on the real head are co-registered with those on the mesh head, movements of the TMS coil relative to the head of the participant in real space are registered online and visualized in real-time at correct positions relative to the participant's anatomical reconstruction of the brain. By superimposing the functional data on the anatomical reconstruction of the brain, the TMS coil can be neuronavigated to a specific anatomical and/or functional activation area of every participant. In contrast to the fMRI group analysis, TMS neuronavigation was based on data in AC–PC space (rotating the cerebrum into the anterior commissure–posterior commissure plane). This was done in order to avoid any additional transformations that could distort the correspondence between MRI and stereotaxic points.

Using this system, we online navigated the TMS coil to the individual activation hot spot as revealed by fMRI for the congruity effect only, and monitored its position accuracy throughout the TMS measurements. This has been done, as we had to choose a single hot spot for stimulation during the behavioral task, in which both size congruity effect and numerical distance effect been computed from. Otherwise, targeting the TMS coil to different foci that showed congruity effect and numerical distance effect would have not allowed examining if both effects derived from the same stimulated area. The same threshold has been used for all participants to identify the activation hotspots [automatic FDR threshold ($q = 0.05$)].

RESULTS

SIZE CONGRUITY EFFECT

As described elsewhere (Cohen Kadosh et al., 2007b), the size congruity effect interacted with TMS. In brief, we observed an interaction between TMS (right, left, or sham) and congruity (congruent, neutral, and incongruent) [$F(4,16) = 4.17$, MSE = 415, $p < 0.05$, $\eta_p^2 = 0.51$]. As illustrated in **Figure 2A**, the size congruity effect decreased after stimulation to the right IPS [56 ms, $F(1,4) = 13.88$, MSE = 1,129, $p < 0.05$, $\eta_p^2 = 0.78$], as compared to no observed effect under the left IPS stimulation [109 ms, $F(1,4) = 12.64$, MSE = 4,654, $p < 0.05$, $\eta_p^2 = 0.76$], or under sham stimulation [90 ms, $F(1,4) = 20.61$, MSE = 1,942, $p < 0.01$, $\eta_p^2 = 0.84$, for a more in depth analysis see (Cohen Kadosh et al., 2007b)]. Here, we focused on a new analysis, comparing the previously established TMS-effects on automatic size congruity performance, with the intentional numerical distance effect calculated on the same data. Please note that the data on the numerical distance effect is independent of the data used to calculate the size congruity effect. That is, albeit the calculation of both effects is based on the same data from the same participants, the calculation of the numerical distance effect is orthogonal to the one used for the size congruity effect. That is, the numerical distance effect includes the comparison between small and large numerical distances across congruity conditions, while the size congruity effect includes the comparison of congruity conditions across small and large numerical distances.

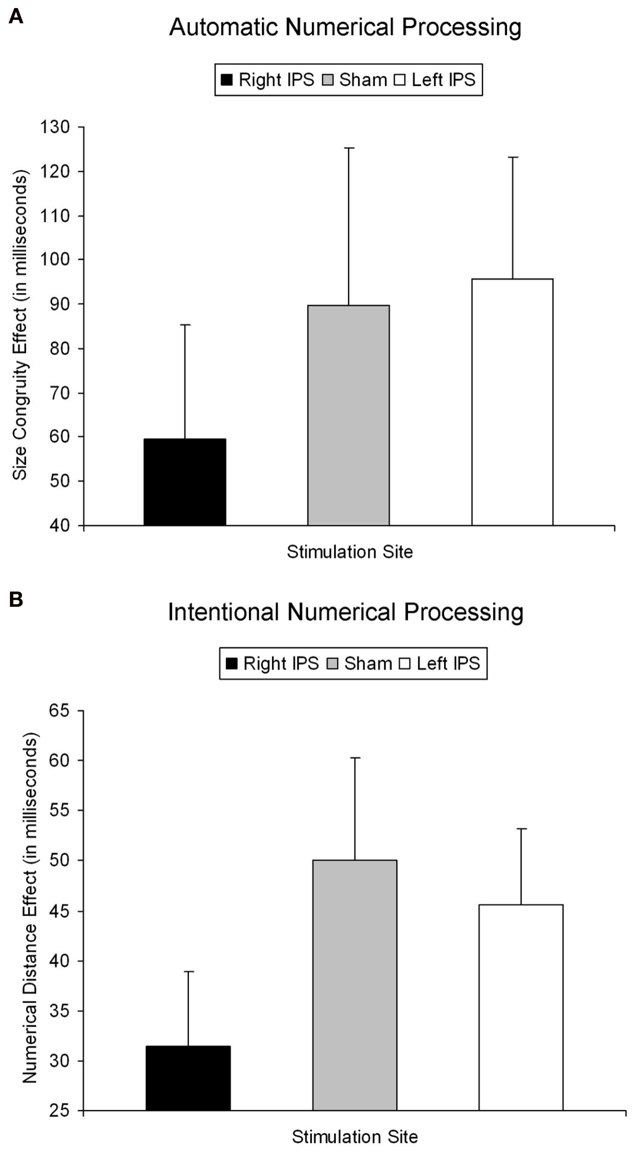

FIGURE 2 | Behavioral effect for automatic and intentional numerical processing [(A,B) respectively]. (A) The size congruity effect for the right IPS, sham, and left IPS stimulation. Only TMS over the right IPS decreased automatic numerical processing as indicated by a significantly reduced size congruity effect. **(B)** The numerical distance effect for the right IPS, sham, and left IPS stimulation. Only TMS over right IPS decreased intentional numerical processing as indicated by a significantly reduced numerical distance effect. Hence, the same functional parietal asymmetry seems to underlie automatic and intentional numerical processing. Error bar reflects one SE of mean.

Numerical distance effect: reaction time

The mean RTs were subjected to a three-way ANOVA with TMS (left IPS, right IPS, or sham), task (physical or numerical comparison), and numerical distance (1-unit or 6-units) as within-subject factors. The main effects for task (physical, 456 ms; numerical, 527 ms) [$F(1,4) = 51.61$, MSE = 1,442, $p = 0.001$, $\eta_p^2 = 0.93$], and numerical distance (1-unit, 501 ms; 6-units, 482 ms) [$F(1,4) = 35.71$, MSE = 153, $p < 0.005$, $\eta_p^2 = 0.9$] were significant. In addition, the interaction between task and numerical distance [$F(1,4) = 33.35$, MSE = 244, $p < 0.005$, $\eta_p^2 = 0.9$], and most importantly, the triple interaction between TMS, task, and numerical distance [$F(2,8) = 8.12$, MSE = 46 $p = 0.01$, $\eta_p^2 = 0.67$, **Table 1** and **Figure 2B**] were significant. The triple interaction was due to a smaller numerical distance effect in the numerical comparison task when the participants received TMS over right IPS (31 ms) compared to TMS over left IPS or sham stimulation (46 and 50 ms, respectively). In contrast, no differences with regard to numerical distance were found for the physical size comparison. We used interaction contrasts analysis (Boik, 1979), a *post hoc*

Table 1 | Reaction time (in milliseconds) a function of TMS, task, and numerical distance.

Numerical distance	Right IPS		Sham		Left IPS	
	Size	**Number**	**Size**	**Number**	**Size**	**Number**
Small	440 (17)	549 (28)	461 (19)	548 (29)	462 (34)	546 (29)
Large	436 (15)	518 (24)	462 (18)	498 (20)	477 (42)	501 (26)

Parentheses: one SE of mean.

analysis of the individual cells of the significant interaction, by giving weights simultaneously to all the relevant variables. In this case one can compare at least two levels in each of the variables at the same time. The interaction contrasts analysis yielded a partial eta square of 0.81 for right IPS TMS vs. left IPS TMS and sham (−2, 1, 1) and the two-way interaction between task and numerical distance [$F(1,4) = 16.87$, $\text{MSE} = 41$, $p = 0.01$]. In contrast, the same analysis of left IPS TMS vs. sham (−1, 1) and the two-way interaction between task and numerical distance yielded a partial eta square of only 0.19 ($F < 1$).

Previous studies have shown that congruity and numerical distance might interact (Schwarz and Ischebeck, 2003; Szucs and Soltesz, 2007; Cohen Kadosh et al., 2008b; Gebuis et al., 2010). When examining whether congruity modulated the triple interaction between TMS, task, and numerical distance, the effect was not significant [$F(4,16) = 1.41$, $\text{MSE} = 904$, $p = 0.27$, for the four-way interaction between TMS, task, congruity, and numerical distance]. Nevertheless, to test whether the current effect was only due to non-neutral trials, we further examined whether the same pattern of the numerical distance effect, as has been obtained for different stimulation sites, was also found for the neutral condition, when no variation in physical size occurred, thus mimicking the more traditional numerical distance effect (Moyer and Landauer, 1967; Holloway and Ansari, 2009). When taking only the neutral trials the same pattern of numerical distance effect has been obtained (including a three-way interaction between TMS, task, distance [$F(2,8) = 3.77$, $\text{MSE} = 284$, $p = 0.07$, $\eta_p^2 = 0.49$]. Namely, the distance effect for right TMS was not significant [14 ms, $t(4) = 0.79$, $p = 0.47$], while it was significant for the sham condition [46 ms, $t(4) = 2.54$, $p = 0.03$, one-tailed, Cohen's $d = 1.18$], and left TMS [54 ms, $t(4) = 5.03$, $p = 0.004$, one-tailed, Cohen's $d = 0.94$].

As described in the introduction, smaller numerical distances have been associated with better intentional processing. We examined whether this was the case in the current experiment. If the smaller numerical distance effect would have stemmed from a decrease in RTs for the 1-unit numerical distance, this would indicate a better intentional processing. However, if the current effect was due to an increase in RTs for the 6-units numerical distance, this would indicate that the current effect originates from impairment in intentional numerical processing. The current results supported the latter possibility. Namely, interaction contrasts analysis yielded a partial eta square of 0.67 for right IPS TMS vs. left IPS TMS and sham (−2, 1, 1) and the contrast between 6-units numerical distance in the numerical task and the physical task (with the latter serving as a baseline of general processing time, as numerical distance did not play any role in physical task (all p's > 0.2; see **Table 1**) [$F(1,4) = 8.16$, $\text{MSE} = 543$, $p < 0.05$]. In contrast, the same analysis of right IPS TMS vs. left IPS TMS and sham (−2, 1, 1) and the contrast between 1-unit numerical distance between the numerical task and the physical task was not significant and yielded a partial eta square of only 0.27 [$F(1,4) = 1.47$, $\text{MSE} = 584$, $p > 0.29$].

These analyses show that TMS over right IPS impaired intentional numerical processing by decreasing the numerical distance effect when participants compared numerical values, as opposed to sham stimulation or stimulation over left IPS, which had no significant effects on behavioral performance.

Numerical distance effect: error rates

The average error rate was 4.3%. In contrast to the significant triple interaction found when comparing RTs, this pattern was not found with regard to behavioral accuracy [$F(2,8) = 0.09$, $\text{MSE} = 0.002$, $p > 0.91$]. In addition, the correlation between RTs and error rates was not significant, but followed the positive trend, thus excluding any speed-accuracy tradeoff explanation [$t(4) = 1.8$, $r = 0.49$, $p > 0.1$, two-tailed].

COMPARING INDIVIDUAL ACTIVATION HOT SPOTS FOR THE SIZE CONGRUITY EFFECT AND THE NUMERICAL DISTANCE EFFECT

To assess whether the current results showed a right IPS, but not left IPS necessity for the size congruity effect and whether the numerical distance effect was due to a larger variability of activation in the left IPS vs. the right IPS, we co-registered the activations for the size congruity effect and the numerical distance effect to Talairach-transformed anatomical data (Talairach and Tournoux, 1988, see Materials and Methods), and projected the individual activation onto a population-averaged human brain using Caret[1] (Van Essen et al., 2001) and SumDB[2] (Van Essen, 2002). The spatial distribution of the size congruity effect and the numerical distance effect in the IPS is presented in **Figure 3** and gives a strong impression against a systematic difference between the right and left IPS. We further examined this issue by using inferential statistics. We entered all activations in the IPS into a three-way ANOVA, with effect (size congruity, numerical distance), hemisphere (left, right), and Talairach coordinates (TCs; X, Y, Z), as within-subjects factors. As indicated from **Figure 3** the main effect for effect, as well as its interaction with other factors including the critical three-way interaction between effect, hemisphere, and TCs [$F(2,8) = 0.15$, $\text{MSE} = 81.4$, $p > 0.85$] was not significant.

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[1] http://brainmap.wustl.edu/caret

[2] http://sumsdb.wustl.edu:8081/sums/directory.do?id = 636032

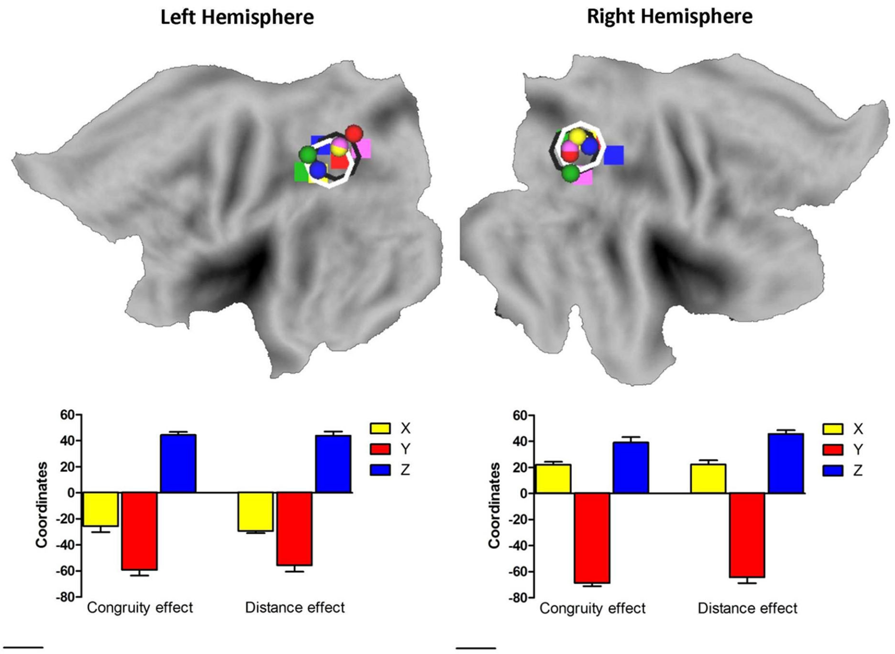

FIGURE 3 | Plotting individual activation hot spot for the size congruity effect and the numerical distance effect. Individual activation hot spot for the size congruity effect (sphere) and the numerical distance effect (rectangular) as used for the TMS neuronavigation study plotted on a flat brain using Caret (Van Essen et al., 2001; Van Essen, 2002). Different colors represent different individuals. As can be seen, the average coordinates for the size congruity effect and the numerical distance effect in each hemisphere show a substantial overlap. This is indicated by the black and white rings in each hemisphere (size congruity and numerical distance, respectively) and by the bottom graphs (each graph depicts the average coordinates from the hemisphere above it).

DISCUSSION

The current study examined whether automatic and intentional numerical processing rely on the same hemispheric asymmetry in the parietal cortex. More concretely, we disrupted either left or right parietal cortex functioning in the same subject sample during automatic and intentional numerical processing to compare the lateralized effects of these TMS-induced parietal "lesions" on both processes. We assessed whether automatic and intentional numerical processing, reflected by the size congruity effect and the numerical distance effect, respectively, are equally or differentially affected by unilateral TMS over the left or right IPS, a key region for numerical cognition (Ansari, 2008; Cohen Kadosh et al., 2008c; Willmes, 2008; Cohen Kadosh and Walsh, 2009; Cappelletti and Cipolotti, 2010; Houde et al., 2010). As previously shown, automatic numerical processing is impaired by right IPS disruption, in contrast to left IPS and sham stimulation which have no effect. If the same pattern would be observed with regard to intentional processing, this would imply similar brain mechanisms or a similar parietal functional asymmetry underlying both functions.

After stimulation over the right IPS we observed impairment in automatic as well as intentional numerical processing. In contrast, sham stimulation and stimulation over the left IPS affected neither automatic, nor intentional numerical processing. This result provides causal evidence for the idea that automatic and intentional processing are based on a shared mechanism, at least within the parietal cortices and in the case of numerical cognition. Note that when discussed mechanism in the current context, we refer to the anatomical level, rather than neuronal level, as it might be that different neuronal populations subserved different processes at the same anatomical level (cf. Cohen Kadosh and Walsh, 2009).

A possible limitation to the current study might have been the small number of subjects, which is not a rare scenario in the case of TMS–fMRI studies (Chambers et al., 2004; Ruff et al., 2006; Sack et al., 2006), as the addition of fMRI, while been more complicated, and expensive, allows to reduce irrelevant variance, and increase to increase the statistical power (Sack et al., 2009). One might argue that ANOVA is not the suitable methods for analysis, due to a possible violation of normality. While some have suggested that violation of normality even with small sample can still lead to meaningful results (Glass et al., 1972), one might suggest to use non-parametric tests, which are less powerful, and those might lead to a type II error. Nevertheless, we also examined whether the current effects can be observed when one use a non-parametric tests. Indeed, in all the cases the numerical distance and effect and the size congruity effect under right TMS did not reach the level of significant, while they were still significant under sham and left TMS. This, together with the fact that the current interactions and pattern of results were obtained for two different effects, increase the validity of the current findings, and reduce the likelihood of a Type I error.

While the coordinates over the left and right IPS were indistinguishable for both automatic and international processing, descriptively, the activation on the right parietal was more diffuse than the left parietal (size congruity effect: left parietal, 1271 voxels, right parietal, 1454 voxels; distance: left parietal, 11499 voxels; right parietal, 14215 voxels). However, these differences were small, and could have biased toward a greater effect over the left hemisphere, as the activation there was more focus, and therefore more amenable to TMS than the more diffuse activation on the right hemisphere. However, at this stage there is no knowledge how (and if) the size of activation correlates with the effect of TMS, and this should be a goal of future methodological studies.

The current results challenge previous findings which reported dissociations between intentional and automatic processing (Kaufmann et al., 2005; Tang et al., 2006; Bugden and Ansari, 2011; Santens and Verguts, 2011). However, it is known that the mere finding of a dissociation does not necessarily imply different underlying mechanisms (e.g., Shallice, 2003). Similarly, neuroimaging studies which reported differential brain activation during intentional and automatic processing provided only correlational evidence. In recent years, neuropsychological studies as well as "virtual" lesion studies using non-invasive functional brain stimulation have shown that brain activation during task execution does not necessarily imply that this brain area is necessary for the given psychological function (Price and Friston, 2002; Walsh and Pascual-Leone, 2003; Bien et al., 2009; Sack, 2009). In contrast, the current study provides strong evidence for a causal relationship between the right, but not left, IPS and the mechanism, which processes numbers both automatically and intentionally.

It must be noted that these results do not rule out the possibility that automatic and intentional processing show a double dissociation in other parts of the brain (e.g., the prefrontal cortex, Cohen Kadosh and Walsh, 2009) or at different time windows than the ones used here, or that automatic and intentional processing of other dimensions (e.g., reading, time perception) might be subserved by different mechanisms. However, what can be concluded here is that the same parietal functional asymmetry seems to underlie both, automatic and intentional numerical processing with only the right, but not left, IPS being causally relevant for successful performance during both tasks. We hope that future studies will take this question further, also in the context of other brain regions or for other cognitive domains, thereby advancing our understanding of the relationship between intentional and automatic processing and various cognitive mechanisms *per se* (Palmeri, 2002; Tzelgov and Ganor-Stern, 2005). Such studies will reveal important insights also for the neural, developmental, and educational bases of automatic vs. intentional processing (Girelli et al., 2000; Rubinsten et al., 2002; Cohen Kadosh and Walsh, 2009; Reis et al., 2009; Rubinsten and Henik, 2009; Bugden and Ansari, 2011).

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Beyond natural numbers: negative number representation in parietal cortex

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Unlike natural numbers, negative numbers do not have natural physical referents. How does the brain represent such abstract mathematical concepts? Two competing hypotheses regarding representational systems for negative numbers are a *rule-based* model, in which symbolic rules are applied to negative numbers to translate them into positive numbers when assessing magnitudes, and an *expanded magnitude* model, in which negative numbers have a distinct magnitude representation. Using an event-related functional magnetic resonance imaging design, we examined brain responses in 22 adults while they performed magnitude comparisons of negative and positive numbers that were quantitatively near (difference <4) or far apart (difference >6). Reaction times (RTs) for negative numbers were slower than positive numbers, and both showed a distance effect whereby near pairs took longer to compare. A network of parietal, frontal, and occipital regions were differentially engaged by negative numbers. Specifically, compared to positive numbers, negative number processing resulted in greater activation bilaterally in intraparietal sulcus (IPS), middle frontal gyrus, and inferior lateral occipital cortex. Representational similarity analysis revealed that neural responses in the IPS were more differentiated among positive numbers than among negative numbers, and greater differentiation among negative numbers was associated with faster RTs. Our findings indicate that despite negative numbers engaging the IPS more strongly, the underlying neural representation are less distinct than that of positive numbers. We discuss our findings in the context of the two theoretical models of negative number processing and demonstrate how multivariate approaches can provide novel insights into abstract number representation.

Keywords: number cognition, symbolic number comparisons, distance effect, integers, negative numbers, intraparietal sulcus, prefrontal cortex, representational similarity

INTRODUCTION

How are abstract mathematical concepts represented in the brain? Negative integers are among the earliest abstract concepts encountered in mathematics curricula. Unlike positive numbers, negative numbers have no obvious perceptual referents, and therefore, children can struggle when learning about them (Liebeck, 1990; Moreno and Mayer, 1999). Nevertheless, most adults can work with negative numbers, making them an ideal test case for investigating the representation of relatively well-developed abstract mathematical concepts. In the past 50 years, researchers have uncovered many behavioral, cognitive, and neural properties associated with positive numbers; much less is known about the representation of negative numbers.

A standard paradigm for investigating mental representations of positive numbers has participants quickly select which of two numbers is quantitatively larger or smaller (Moyer and Landauer, 1967). A consistent finding is that participants are slower to decide among near distance pairs (2 vs. 4) than far distance pairs (2 vs. 9). This distance effect is thought to reflect an analog magnitude representation for positive numbers that follows Weber's law (Dehaene, 2003). Research on negative integers has also shown similar distance effects. For example, Tzelgov et al. (2009) manipulated distance as a continuous variable (from 1 to 8) and found parallel linear slopes for positive and negative numbers, but longer overall reaction times (RTs) for negative numbers. Varma and Schwartz (2011) compared near distance pairs (distance of 2 or 3) and far distance pairs (distance of 7 or 8), and found parallel distance effects for negative and positive numbers, with increased overall RT for negatives. Consistently, participants are slower for negative than positive numbers, even when polarity is marked by font color instead of a sign (Tzelgov et al., 2009) and when sign and number are presented sequentially (Ganor-Stern et al., 2010).

Two general accounts of negative number processing have been proposed in the behavioral literature (Varma and Schwartz, 2011). Each provides a different account to explain the findings that negative numbers show a distance effect and take longer to compare than positive numbers. The first proposes that participants reason about negative numbers by applying abstract rules on top of an existing magnitude representation of positive integers (Fischer and Rottman, 2005; Shaki and Petrusic, 2005; Ganor-Stern and Tzelgov, 2008; Tzelgov et al., 2009). In this *rule-based* model, negative numbers are first transformed into positive numbers for magnitude comparison, and individuals do not represent negative number magnitudes in their own right. The application of rules explains why the negative numbers take longer to compare than the positives. Supporting the rule-based account, Fischer and Rottman (2005) found that when judging whether a number was above or below zero, participants' RTs were affected by the absolute magnitude of the number for positives, but not for negatives. This suggests that for negatives, participants were only considering polarity, while for positives they considered magnitude. Additionally, Ganor-Stern and Tzelgov (2008) and Tzelgov et al. (2009) explored the semantic congruence effect with positive and negative numbers. In this effect, participants are faster to make "lesser" magnitude judgments for small numbers and "greater" judgments for large numbers. The authors found a semantic congruence effect for positive comparisons but not for negative comparisons. Fischer and Rottman (2005) looked at the SNARC effect, in which participants are faster to make parity judgments with their left hands for small numbers and with their right hand for large numbers. They found a traditional SNARC effect for positive numbers, but an inverse SNARC effect for negative numbers. Participants were faster to use their left hands to make parity judgment responses for large negatives (e.g., −1), and faster to use their right hand to respond to small negatives (e.g., −9). This finding suggests that participants may strip the sign from the negative number and make judgments about the resulting positive numbers. These results are consistent with the proposal that participants use rules to process negative numbers.

The second, *expanded magnitude,* model proposes that negative numbers are represented as magnitudes in their own right (Fischer, 2003; Varma and Schwartz, 2011). In this model, "−3" is encoded as a magnitude distinct from "3." However, because most individuals have considerably less experience with negative numbers, the representations for negative numbers may be less-refined than those of positive numbers. By this account, negative numbers take longer to compare than positives because they have less resolution (Varma and Schwartz, 2011). Supporting an expanded magnitude model, Fischer (2003) found that when adults compared two negative numbers, they were faster when the digit magnitudes followed the canonical order of the number line (e.g., −9, −4), than when ordered by absolute value (e.g., −4, −9). In contrast to Tzelgov and colleagues (Ganor-Stern and Tzelgov, 2008; Tzelgov et al., 2009), Varma and Schwartz (2011) found a polarity-dependent semantic congruence effect. For positives, participants were faster to judge the greater number, and for negatives, they were faster to judge the lesser number. This suggests negatives are considered small in comparison to positive numbers. Additionally, for mixed magnitude comparisons which involved a positive and a negative number, Varma and Schwartz (2011) and Krajcsi and Igacs (2010) found an inverse distance effect, with faster RTs for near comparisons, suggesting that people are reasoning about magnitude and not only focusing on polarity in mixed comparisons (but see Tzelgov et al., 2009 for studies which failed to find distance effects for mixed comparisons).

In sum, the behavioral research has been inconclusive with respect to the representation of negative numbers, with several studies supporting each of the leading models. One explanation of this inconsistency is that adults have multiple ways of interacting with negative numbers dependent on the task at hand (Ganor-Stern et al., 2010; Varma and Schwartz, 2011). For example, Shaki and Petrusic (2005) found an inverse SNARC effect when positive and negative comparisons were presented in separate blocks, consistent with a rule-based account. However, they found a standard SNARC effect, consistent with an extended magnitude account, when positive and negative comparisons were intermixed. When negative trials are presented in a block, participants may adopt a rule-based strategy, knowing it will work efficiently for all trials. In contrast, intermixing negative and positive trials may lead participants to consider magnitude for each trial, because they cannot rely on a single rule across trials.

The current study explores the neural correlates of negative number processing in the context of a symbolic magnitude comparison task where positive and negative trials are intermixed. The intraparietal sulcus (IPS) within the dorsal aspects of the posterior parietal cortex has been implicated in numerical processing of positive numbers. IPS activation has also been found more generally for tasks requiring spatial attention and serialization (Majerus et al., 2007; Egner et al., 2008) and there is some controversy about the specificity of the IPS for numerical magnitude processing (Shuman and Kanwisher, 2004; Ansari et al., 2005; Cohen Kadosh et al., 2008b). Among the strongest evidence for its role in numerical processing is that IPS responses are consistently modulated by numerical distance between positive numbers. In symbolic number comparison tasks, where spatial attention demands are held constant, functional magnetic resonance imaging (fMRI) and ERP studies have demonstrated that activation in the IPS is modulated by distance between the numbers, with near pairs eliciting greater IPS activity than far pairs (Pinel et al., 2001; Gobel et al., 2004; Ansari et al., 2005; Kaufmann et al., 2005). This "neural distance effect" is also found in the IPS when non-symbolic numerosity is manipulated (Piazza et al., 2004; Ansari and Dhital, 2006; Kaufmann et al., 2008; Cantlon et al., 2009) and when comparing perceptual features, such as the physical size and luminance of symbols (Pinel et al., 2004; Cohen Kadosh et al., 2005, 2007, 2008a; Kaufmann et al., 2005).

Very little is currently known about "neural distance effects" for negative numbers in the IPS and or other brain areas like the prefrontal cortex, which is sensitive to task difficulty and rule-based processing. To our knowledge no previous neuroimaging study has explicitly manipulated numerical distance on comparisons with negative numbers. Based on the positive integer literature, we expect negative number processing to rely on the IPS. An important question is whether negative number processing engages this area differentially from the positive numbers. One imaging study to date has examined the representation and processing of negative numbers. Chassy and Grodd (in press) used a block fMRI design to investigate neural activity evoked by four increasingly abstract comparison tasks. In separate blocks, participants compared the size of disks, the number of dots, positive integers, and negative integers. Dots and positives ranged from 1 to 9, and negatives ranged from −1 to −9. Specific distance comparisons were randomly selected from all possible combinations. A conjunction analysis revealed that all four comparison tasks activated the bilateral IPS. The authors found greater activity for negative, vs. positive, number comparisons in the superior orbital gyrus. Surprisingly, there was no differential activation of the IPS or any other subdivision of the lateral parietal and prefrontal cortices for negative over positive numbers. Notably, the authors did not examine numerical distance effects.

In the current study, we used event-related fMRI to investigate the processing and representation of negative and positive numbers. A factorial design crossed number type (positive vs. negative vs. mixed) and distance (near vs. far). A univariate analysis explored the neural correlates of number type and distance, and we discuss the results in relation to the two competing models of integer representation. A complication in interpreting the results of signal level differences between negative and positive comparisons is that negative comparisons take longer than positives, and signal level differences could be due to longer processing time. Thus, it is critical to address the extent to which activation differences reflect neural responses specific to negative number processing, as opposed to general task difficulty.

We complemented traditional univariate analyses of signal change with a representational similarity analysis (RSA), a multivoxel approach for examining stimulus-related brain responses (Kriegeskorte et al., 2008). RSA assesses the voxel-wise correlation between the activation patterns of two task conditions within an ROI. Because RSA is based on correlation of spatial activity patterns, it is independent of overall activation differences between conditions. This allows us to examine number representations independent of the effect of RT on signal level. Here, we examine the similarity of spatial activity patterns for near and far comparisons within positive and negative trials. If negative numbers have a less-refined representation of magnitude, there should be higher similarity between near and far problems for negative, compared to positive numbers. In this view, the negative numbers do not have an equally well-developed differentiation of small and large magnitudes, leading to greater overlap in their representations. In contrast, if negative number comparison relies on the magnitude representation of positive numbers, the *rule* hypothesis would predict that the similarity between near and far comparisons should be the same across negatives and positives. RSA provides a complementary, multivariate measure of neural distance effects, instantiated as representational distinctiveness between near and far trials.

To further investigate number representation in the IPS in an anatomically unbiased manner, we used cyto-architectonically defined maps to quantify both the overall level of activity (Wu et al., 2009; Chassy and Grodd, in press; Rosenberg-Lee et al., 2011) and RSA (Ashkenazi et al., in press). Observer independent cyto-architectonic mapping methods have revealed three distinct subdivisions of the IPS in each hemisphere. In the anterior to posterior direction they are hIP2, hIP1 (Choi et al., 2006), and hIP3 (Scheperjans et al., 2008). Together, the univariate and multivariate approaches allowed us to probe differential neural responses and representations to negative numbers in greater depth than has been possible.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-two right-handed individuals (16 females), mean age 24.2 (SD 6.8), participated in the study. Three additional participants were excluded due to technical problems during data collection (two participants), or failure to complete the study (one participant). Participants were drawn from a paid subjects pool, and were compensated for their participation. All participants provided written informed consent in compliance with Stanford University's Human Research Protection Program.

TASK DESIGN AND STIMULI

The study design was modeled on behavioral research by Varma and Schwartz (2011). Two single-digit integers were displayed on a screen. Participants indicated the greater (or lesser) of the two numbers by pressing a button on a button box. The greater/lesser task demand alternated between blocks, with the order counterbalanced across participants. Problems were of three types (intermixed within runs): In *positive* comparison problems, both numbers were positive (e.g., 6, 8). In *negative* comparisons, both were negative (e.g., −6, −8). In *mixed* comparisons, one number was positive and the other negative (e.g., −6, 2). Distance was also manipulated, such that half of the problems of each type were *near* comparisons and half were *far* comparisons. In near comparisons, the difference between the numbers was two or three (e.g., 7, 9). In far comparisons, the difference was seven or eight (e.g., 2, 9). All problems are presented in **Table 1**.

Stimuli were presented in four runs using a fast event-related design. There were 72 trials in each run, yielding 288 total trials (48 per condition). Within each run, participants saw an equal number of trials from all six conditions, presented in a random order. Left/right configuration of the digits (e.g., 2, 7 vs. 7, 2) was counterbalanced within each run. For the far trials, each problem was repeated twice within a run, in each configuration, because there are fewer possible problems of distance seven or eight among the single digits.

Stimuli were displayed using E-prime presentation software (Psychological Software Tools, Pittsburgh, PA, USA), and were projected onto a screen at the head of the scanner bore. Participants viewed the screen through a mirror directly in their line of vision. The two digits were presented in green on a black background, equidistant from the center of the screen. Participants held a button box in their right hand and indicated which number was greater (or lesser) by pressing their index finger to choose the number on the left, and their middle finger to choose the number on the right. Before each stimulus was presented, participants saw a blank screen, jittered between 0.5 and 5.5 s, in 100 ms increments. Participants then saw a center fixation cross for 500 ms, followed by the stimulus, which was present for 1500 ms (see **Figure 1**).

Prior to entering the scanner, participants completed a brief 20 problem training session. At the beginning of each run in the scanner, two short instruction screens reminded the participants of the task and informed them whether they were making a greater

Table 1 | Experimental stimuli for each number type and distance.

	Positive	Negative	Mixed
Near	[(1, 3); (1, 4); (2, 4) (6, 8); (6, 9); (7, 9)]^a	[(−1, −3); (−1, −4); (−2, −4) (−6, −8); (−6, −9); (−7, −9)]^a	[(1, −2); (−1, 2); (−1, 1)]^b
Far	[(1, 9); (1, 8); (2, 9)]^b	[(−1, −9); (−1, −8); (−2, −9)]^b	[(1, −6); (−1, 6); (1, −7) (−1, 7); (2, −6); (−2, 7)]^a

[a] Stimuli repeated two times per run; [b] stimuli repeated four times per run.

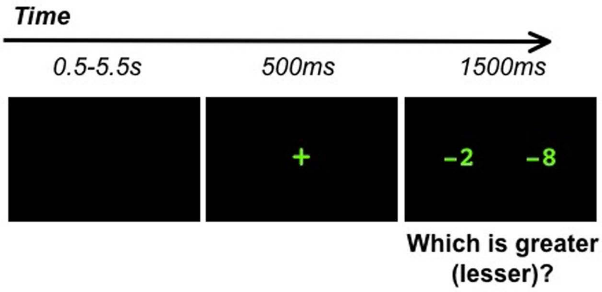

FIGURE 1 | Task timing. Each trial began with a variable fixation period (0.5–5.5 s), followed by a fixation cross (500 ms) and presentation of two numbers for magnitude comparison (1500 ms).

or lesser judgment for the run. Participants then completed two unrecorded practice trials. Data collection began after the practice trials and lasted 5 min and 38 s. Thus, the time between the instructions and the first trial was approximately 20 s, including 14 s for signal equilibration and the initial jitter period.

fMRI DATA ACQUISITION

Images were acquired on a 3-T GE Signa scanner using a standard GE 8-channel head coil (software Lx 8.3). Head movement was minimized during scanning with small cushions fit between the head and the coil. A total of 30 axial slices (4.0 mm thickness, 0.5 mm spacing) parallel to the AC–PC line and covering the whole brain were imaged using a T2* weighted gradient echo spiral in/out pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 80°; Glover and Lai, 1998). The field of view was 20 cm, and the matrix size was 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional MRI scans (Kim et al., 2002).

fMRI DATA ANALYSIS

Preprocessing

The first seven volumes were discarded to allow for signal equilibration effects. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover and Lai, 1998). Functional MRI data were then analyzed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm).

Images were realigned to the first scan to correct for motion and slice acquisition timing. Images were spatially normalized to standard MNI space using the echo-planar imaging template provided with SPM8, resampled every 2 mm using trilinear sinc interpolation, and smoothed with a 6-mm full-width half-maximum Gaussian kernel to decrease spatial noise prior to statistical analysis. Translational movement in millimeters (x, y, z) and rotational motion in degrees (pitch, roll, yaw) was calculated based on the SPM8 parameters for motion correction of the functional images in each subject. No participant had movement greater than ±3 mm translation or ±3° of rotation.

Univariate individual and group analysis

Statistical analysis was performed on individual and group data using the general linear model implemented in SPM8. Task-related regressors were modeled as boxcar functions corresponding to each condition. There were six regressors (three number types × two distances) for the correct trials, with one additional regressor for all incorrect trials. Additionally, the six movement parameters generated from the realignment procedure were included as regressors of no interest. Regressors of interest were convolved with a hemodynamic response function and a time derivative to account for voxel-wise latency differences in hemodynamic response. Low-frequency drifts at each voxel were removed using a high-pass filter (0.5 cycles/min) and serial correlations were accounted for by modeling the fMRI time series as a first degree autoregressive process (Friston et al., 1997).

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure (Holmes and Friston, 1998). Group level activation was determined using individual subject contrast images and a second-level random-effects analysis. At the group level, one sample t-tests were computed using the following individual level paired-sample t-tests (1) Number Type (positive vs. negative); (2) Distance (Near vs. Far); and (3) the interaction of Number type and Distance. After gray matter masking, significant activation clusters were determined using a height threshold of $p < 0.001$, and an extent threshold of 30 voxels was determined using Monte Carlo simulations and a family wise error (FWE) correction for multiple comparisons at $p < 0.05$ (Forman et al., 1995; Ward, 2000).

In each iteration of the Monte Carlo procedure, a 3-D image with the same resolution and dimensions as the fMRI scan was randomly generated and smoothed with a 6-mm FWHM Gaussian kernel for consistency with the inclusive mask used to report the results of the general linear model analysis. A gray matter mask was then applied to this image. The maximum cluster size at a given height threshold was recorded for each iteration, and 10,000 iterations were performed. At a height threshold of $p < 0.001$, less than 5% of the iterations had a maximum cluster size greater than 30 voxels.

Functionally defined regions of interest were compared to cyto-architectonic maps of parietal cortex, using the Anatomy Toolbox in SPM8 (Eickhoff et al., 2005). This toolbox computes three statistics to characterize the overlap between functional and structural regions: (1) the number of voxels in the functional cluster which overlap with a structural ROI, (2) the percentage of the functional cluster that overlaps with the structural ROI, and (3) the percentage of the structural ROI that overlaps with the functional ROI. These measures are needed to fully characterize clusters of differing size.

Region of interest analyses

Two sets of ROIs were identified: (1) Functional ROIs were constructed using 10 mm spheres centered at the peaks of significant activation in the paired-sample *t*-tests. (2) Unbiased anatomical ROIs were created based on cyto-architectonically distinct subdivisions of the IPS (Eickhoff et al., 2005). Three distinct subdivisions of the IPS have been identified: hIP2 on the anterior lateral bank, hIP1 which is anterior and lateral compared to hIP2 (Choi et al., 2006), and hIP3 which is posterior to both regions (Scheperjans et al., 2008). These subdivisions have previously been used to map activation in arithmetic tasks (Wu et al., 2009; Rosenberg-Lee et al., 2011). For each ROI, average beta scores for the contrasts of negative number comparisons vs. rest and positive number comparisons vs. rest were entered into a repeated measures ANOVA. As a control analysis, an ANCOVA model with RT differences (Negative RT–Positive RT) as a between-subjects covariate was used to investigate whether activation differences between negative and positive number processing arose from RT differences.

Representational similarity analysis

Representational similarity analysis (RSA) considers the voxel-wise similarity between the activation patterns of task conditions within an ROI (Kriegeskorte et al., 2008). Using the individual *t*-maps employed in the univariate group analyses, we computed Pearson correlations between the near and far problems for positive trials and again separately for negative trials. This correlation represents the spatial similarity in activation patterns between the two conditions, independent of overall activation level. The individual *r*-values were transformed to a normal distribution using Fisher's *r*-to-*z* transformation: $z_{i,j} = 0.5 \times \ln((1 + r_{i,j})/(1 - r_{i,j}))$. RSA correlations were computed in each functional and anatomical ROI.

RESULTS

BEHAVIORAL

Accuracy

Across all cells of the design, average accuracy was above 90%. Accuracy data were analyzed using a three Number Type (positive, negative, mixed) × 2 Distance (near, far) repeated measures ANOVA. There was a main effect of number type [$F(2,42) = 20.0$, $p < 0.001$]. There was no main effect of distance [$F(1,21) = 1.5$, $p = 0.230$], and a marginal number type by distance interaction [$F(2,42) = 2.9$, $p = 0.065$]. *Post hoc* comparisons using the Tukey HSD test at the $p < 0.05$ level revealed that participants were significantly more accurate on mixed comparisons than positive comparisons, which were more accurate than negative comparisons (see **Figure A1** in Appendix). *Post hoc* investigation of the number type by distance interaction for negative and positive trials showed that for far comparisons, there were no accuracy differences between negative and positive trials [$t(21) = -0.84$, $p = 0.410$]. However, negative near comparisons were significantly less accurate than positive near comparisons [$t(21) = -3.6$, $p = 0.002$, see **Figure 2**].

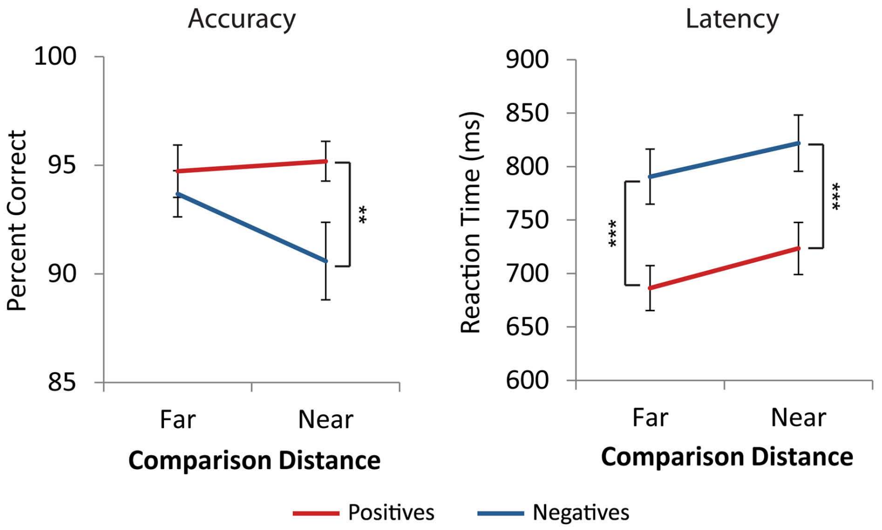

FIGURE 2 | Behavioral performance. Participants were less accurate on near comparisons with negative numbers than positive numbers (**$p < 0.01$), but did not differ on far comparisons. Participants were slower on negative problems than positive problems for both near and far comparisons (***$p < 0.001$). Error bars represent ±1 SE.

Response time

For each participant, the mean RT and SD on correct trials were computed for each number type and distance. RTs more than 2.5 SD from the individual mean were removed. A three Number Type (positive, negative, mixed) × 2 Distance (near, far) repeated measures ANOVA revealed a significant main effect of number type, [$F(2,42) = 180.0$, $p < 0.001$], a main effect of distance, [$F(1,21) = 37.7$, $p < 0.001$], and a number type by distance interaction, [$F(2,42) = 9.8$, $p < 0.001$]. *Post hoc* analysis using the Tukey HSD test at the $p < 0.05$ level revealed that negative comparisons were significantly slower than positive comparisons, which were slower than mixed comparisons. The effect of distance was significantly different for mixed comparisons than for positive and negative comparisons [$F(1,21) = 22.9$, $p < 0.001$],which did not differ from each other [$F(1,21) = 0.36$, $p = 0.556$, see **Figure A1** in Appendix]. t-Tests confirmed that there were distance effects, i.e., near comparisons were slower than far comparisons, for positive [$t(21) = 5.4$, $p < 0.001$] and negative comparisons [$t(21) = 4.2$, $p < 0.001$] but not the mixed comparisons [$t(21) = 0.1$, $p = 0.890$, see **Figure A1** in Appendix]. Additionally, for both near and far comparisons negative trials were significantly slower than positive trials [$t(21) = 13.3$, $p < 0.001$, $t(21) = 12.2$, $p < 0.001$, see **Figure 2**].

BRAIN IMAGING: WHOLE BRAIN UNIVARIATE ANALYSIS

Mixed trials are not considered further in the main text because they failed to show the classic indicator of magnitude processing, differential RTs for near and far comparisons. These trials may have been solved with the strategy of identifying a negative sign to find the smaller number without considering magnitude. Here we focus on pure negative and positive comparisons, which did show robust distance effects. GLM results comparing mixed vs. positive and negative trials are presented in the Appendix (**Table A1** in Appendix).

Negative numbers elicit greater fMRI signal than positive numbers in distributed cortical regions

Compared to positive numbers, negative numbers elicited greater activity in the bilateral middle frontal gyrus (MFG), pre-supplementary motor area (**Figure 3A**), and bilateral inferior occipital cortex and the lingual gyrus (**Figure 3B**). Three clusters in the left IPS and one in the right IPS also had greater activity for negative over positive numbers (**Figure 4**). The IPS regions tended to overlap with hIP1 and hIP3 subdivisions of the parietal cortex (**Table A2** in Appendix). Only the posterior cingulate cortex showed greater activity for positive numbers relative to negative numbers, but this difference arose from greater deactivation to negative numbers (**Figure 4**). **Table 2** provides further details about all functional clusters that showed differences between negative and positive numbers.

Because RTs are longer for negative than positive trials, greater activity for negative numbers could be driven by task difficulty. To test this possibility, in each brain region that showed differences between negative and positive numbers (**Table 2**) we conducted a repeated measures ANCOVA with the difference in RT between negative and positive as a covariate. None of the differences between negative and positive numbers remained significant in any of the ROIs ($p > 0.196$). There were no significant interactions between RT difference and number type in any ROI ($ps > 0.130$).

Near trials elicit greater fMRI activity than far trials in premotor and somatosensory cortex

Collapsing across negative and positive numbers, near trials showed increased activation over far trials in the left premotor cortex and bilateral somatosensory cortex (SC) extending posteriorly into the superior parietal lobe (SPL; **Table 3**). In the left premotor cortex, differences reflect greater activation for near, compared to far, trials, with both trial types showing activation above baseline. In the bilateral SC/SPL, there was greater activation for near, compared to far, trials, but neither differed from baseline.

Number type interacts with distance in right temporal–occipital fusiform cortex

For the interaction between number type and distance, only the right temporal–occipital fusiform cortex (TOF) was statistically significant, but this effect was driven by differential levels of deactivation rather than greater activation during number comparison (**Figure 5**).

BRAIN IMAGING: ROI ANALYSES

Left IPS regions of interest show marginally significant effects of distance for negative numbers

We examined differential responses in six anatomically defined IPS subdivisions (left and right hIP1, hIP2, hIP3) derived from previous cyto-architectonic mapping studies (Choi et al., 2006; Scheperjans et al., 2008). A four-way repeated measures ANOVA was conducted using activation level measures based on beta parameter estimates, with number type, distance, ROI, and hemisphere as within-subjects factors. There was a significant main effect of number type [$F(1,21) = 11.4$, $p = 0.003$], with negative numbers showing greater activation than positive numbers. There was no main effect of distance, ROI, or hemisphere. However there was a significant number type by distance by hemisphere interaction [$F(1,21) = 5.6$, $p = 0.028$]. Combining the IPS sub-regions, *post hoc* analysis revealed that for negative numbers, the left IPS showed a marginally significant distance effect [$t(21) = 2.0$, $p = 0.059$], but the right did not. There were no significant distance effects for positive numbers in either left or right IPS. In the four-way ANOVA there were no other significant interactions with distance (all $ps > 0.37$) (**Figure 6**).

BRAIN IMAGING: REPRESENTATIONAL SIMILARITY ANALYSIS

IPS has distinct distance representations for positive and negative numbers

We used RSA to examine similarity of IPS response patterns to near and far trials. RSA between these two trial types was computed separately for positive and negative numbers.

Functionally derived ROIs. We first examined RSA in four functional ROIs defined as 10mm spheres around activation peaks of the IPS regions that showed greater activation to negative vs. positive numbers. The left IPS ROI centered at ($-30, -52, 38$) showed a greater near–far similarity for negative numbers than for positive numbers [$t(21) = 3.2, p = 0.004$]. This effect was still significant at $p < 0.05$, after applying a Bonferroni correction for multiple comparisons over the four parietal ROIs (**Figure 7A**). Furthermore, in this region, within negative numbers, individual differences in representational similarity was correlated with RTs ($r = 0.458$, $p = 0.032$), such that more distinct representations were associated with faster RTs (**Figure 7B**).

Cyto-architectonically defined ROIs. Additional analyses were conducted using the six (three in each hemisphere) cyto-architectonically defined IPS ROIs described in the previous

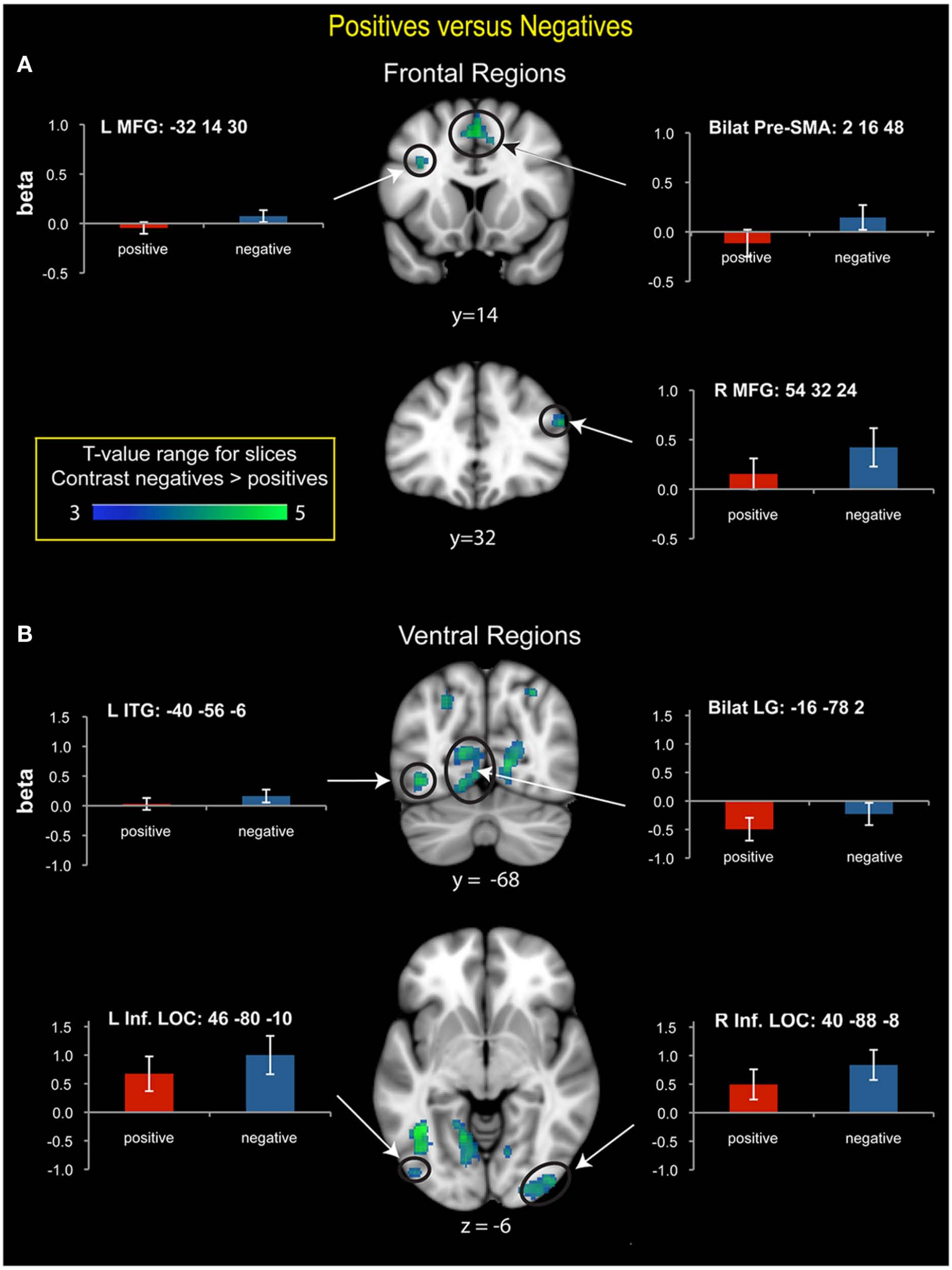

FIGURE 3 | Brain regions that showed significant differences in activation between positive and negative numbers. (A) Frontal regions. Negative numbers had greater prefrontal cortex activation bilaterally in the middle frontal gyrus (MFG) and the pre-supplementary motor area (SMA). In the right MFG, beta value plots reveal activation above baseline for negative numbers, but not for positive numbers. **(B)** Ventral visual regions. Greater activation for negative numbers was detected in the bilateral lingual gyrus (LG), which was driven by greater deactivation for positive numbers. In the bilateral inferior lateral occipital cortex (LOC) there was strong activation above baseline for both number types, with greater activation for negative numbers. In the left inferior temporal gyrus (ITG), activation was greater for negative numbers, though it did not differ from baseline for either number type.

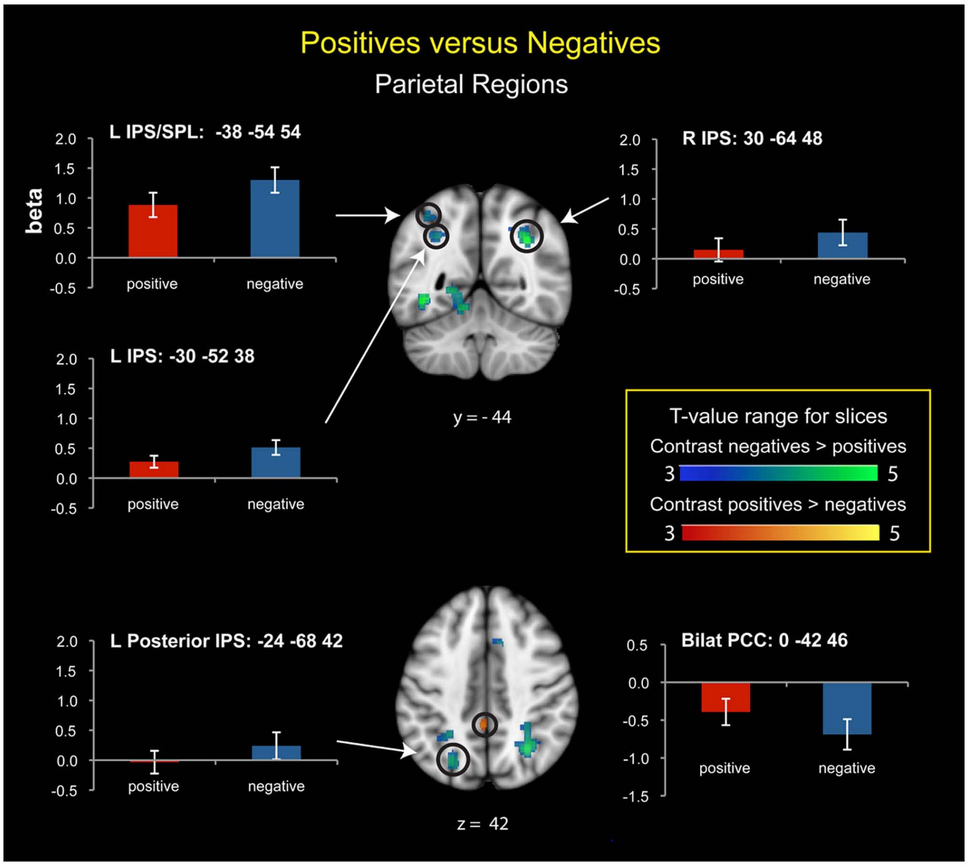

FIGURE 4 | Posterior parietal cortex regions that showed significant activation differences between positive and negative numbers. In the anterior left intraparietal sulcus (IPS) and superior parietal lobule (SPL), there was strong activation for both number types, with greater activation for negative numbers. In the posterior left IPS, there was stronger activation for negative than positive numbers, though neither differed from baseline. In the right IPS, there was significant activation for negative numbers; positive numbers did not differ from baseline. The posterior cingulate cortex (PCC) showed greater deactivation to negative compared to positive numbers.

section. A repeated measures ANOVA with number type (negative, positive), ROI (hIP1, hIP2, hIP3), and hemisphere (L, R) as within participant factors revealed a significant effect of ROI [$F(2,42) = 3.42$, $p = 0.042$]. There was no main effect of number type or hemisphere, but there was a marginal number type by ROI interaction [$F(2,42) = 3.12$, $p = 0.054$]. To further explore this marginally significant interaction, we used a *post hoc* ANOVA to examine differences between number types separately for each ROI. The F-tests revealed that representational similarity was greater within negative than positive numbers in hIP1 [$F(1,21) = 5.6$, $p = 0.027$], but did not differ in hIP2 and hIP3 ($ps > 0.26$). Furthermore, in the left hIP1, representational similarity within negative numbers was again correlated with RTs ($r = 0.508$, $p = 0.016$), such that the more dissimilar the representation of near and far negative trials, the faster the RT (**Figure 8**), although this effect was not significant when using a Bonferroni correction to control for six comparisons. No such association was found between RT and representational similarity in the IPS for positive comparisons in either the functional or cyto-architectonic ROIs (all $ps > 0.57$).

DISCUSSION

While a large body of neuroscience research has addressed the representation of positive numbers, much less is known about the negative numbers. In this study, we examined neural responses and representations of negative integers using traditional univariate analyses and a novel multivariate analysis of representational similarity. To our knowledge, this is first brain imaging study to use a distance manipulation to investigate the representation of negative numbers. Compared to positives, negative number comparisons elicited greater activation in several parietal, frontal, and occipital regions, including bilateral IPS, bilateral MFG, and bilateral LOC. Univariate analyses failed to reveal strong neural distance effects in the IPS, but the multivariate RSA revealed a less differentiated representation for negative, compared to positive, numbers. Furthermore, neural representations were associated with individual differences in performance such that individuals with more distinct neural representations of negative magnitudes performed faster.

The IPS is crucial to positive number processing, and in the following sections, we focus on the role of the IPS in negative number processing, first in terms of overall signal levels and then in terms of multi-voxel representations. Next, we consider the potential role of the prefrontal cortex in the rule-based processing of negative numbers. Finally, we discuss our findings in the context of the previous behavioral research on negative numbers and demonstrate how multivariate approaches can provide novel insights into abstract number representation.

IPS RESPONSE TO NEGATIVE AND POSITIVE INTEGER COMPARISON

Both positive and negative numbers elicited robust bilateral activity in the IPS. For negative numbers compared to positive numbers, whole brain analyses revealed greater activity in a distributed set of regions within the IPS, specifically three clusters in the left IPS and one cluster in the right (**Figure 4**). In contrast to these findings, the only other study of negative number processing to date (Chassy and Grodd, in press) found bilateral IPS activation for negative numbers, compared to fixation baseline, but not when activation to negative and positive numbers were directly compared. In cytoarchitectonic ROIs (Choi et al., 2006; Scheperjans et al., 2008), we found significant activation for negative, compared to positive, numbers in all three IPS subdivisions bilaterally (**Figure 6**). The bilateral IPS is consistently activated in studies of symbolic and non-symbolic natural number processing (see Arsalidou and Taylor, 2011, for a review), and our results extend previous findings on positive number comparisons (Pinel et al., 2001; Ansari et al., 2005; Kaufmann et al., 2005) to negative numbers.

Table 2 | Brain areas that showed differences in activation to negative and positive numbers.

Brain region	Peak MNI coordinates			Peak *t*-value	No. of voxels
	x	*y*	*z*		
POSITIVE TRIALS > NEGATIVE TRIALS					
Bilat PCC	0	−42	46	4.65	87
NEGATIVE TRIALS > POSITIVE TRIALS					
Left ITG	−40	−56	−6	5.64	237
Right IPS	30	−64	48	5.43	396
Bilat pre-SMA	2	16	48	5.36	147
Bilat LG	−16	−78	2	5.27	1621
Right inferior LOC	40	−88	−8	4.67	215
Left IPS	−30	−52	38	4.65	89
Left posterior IPS	−24	−68	42	4.46	84
Right MFG	54	32	24	4.43	35
Left MFG	−32	14	30	4.4	40
Left inferior LOC	−46	−80	−10	4.16	49
Left SPL/IPS	−38	−54	54	4.11	44

PCC, posterior cingulate cortex; ITG, inferior temporal gyrus; IPS, intraparietal sulcus; SMA, supplementary motor cortex; LG, lingual gyrus; LOC, lateral occipital cortex; MFG, middle frontal gyrus; SPL, superior parietal lobule.

Negative numbers took longer to process, suggesting that task difficulty may drive differences in activation to negative and positive numbers. Indeed, after covarying out RT, we found no differences between negative and positive numbers, highlighting the difficulty of disentangling general task difficulty effects from polarity-specific processing. Similar findings likely apply in the domain of positive number comparisons, where near distance comparisons are known to have longer RT and elicit greater activation in the IPS compared to far number comparisons. Few studies have considered whether these effects are independent of RT differences (Gobel et al., 2004; Ansari et al., 2005; Kaufmann et al., 2005). Further studies are needed to examine the relation between IPS activation and RT in both number types, for example by matching RT on specific sets of trials. RSA, which is independent of overall signal level differences, provides a complementary approach to this problem, as discussed below.

STRONG BEHAVIORAL AND WEAK VOXEL-WISE NEURAL DISTANCE EFFECTS FOR POSITIVE AND NEGATIVE NUMBERS

Behavioral distance effects are thought to reflect an analog magnitude representation of positive numbers (Moyer and Landauer,

Table 3 | Brain areas that showed an effect of distance and an interaction of number type by distance.

Brain region	Peak MNI coordinates			Peak *t*-value	No. of voxels
	x	*y*	*z*		
MAIN EFFECT OF TYPE					
Near > far					
Left premotor cortex	−28	−18	72	4.76	49
Left SPL/somatosensory	−34	−42	70	4.68	71
Right SPL/somatosensory	36	−38	70	4.46	39
Far > near					
No significant clusters					
INTERACTION OF TYPE BY DISTANCE					
Negative (near–far) > positive (near–far)					
Right TOF	28	−48	−12	4.71	40
Positive (near–far) > negative (near–far)					
No significant clusters					

SPL, superior parietal lobule; TOF, temporal occipital fusiform.

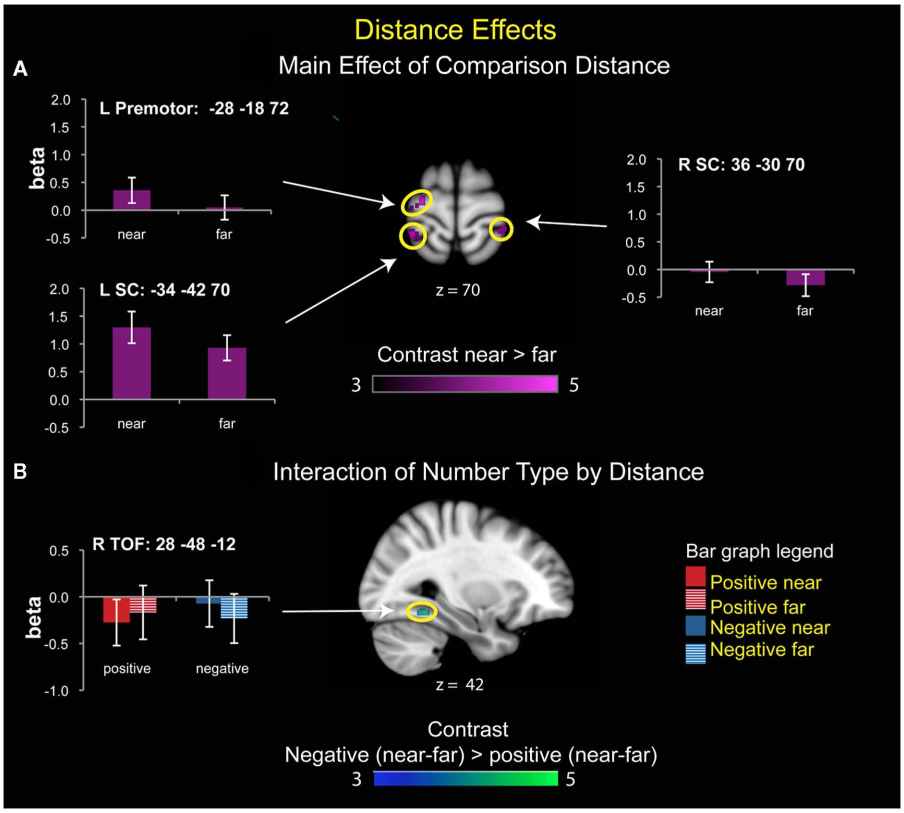

FIGURE 5 | Brain areas that showed significant effects of distance. (A) Main effect of distance. Left premotor cortex and bilateral somatosensory cortex (SC) showed greater activity for near than far comparisons. **(B)** Number type by distance interaction. There was a significant interaction of distance with number type in the right temporal–occipital fusiform cortex (TOF), reflecting greater deactivation for near than far comparisons for positive numbers, and greater deactivation for far than near comparisons for the negative numbers.

1967) and neural distance effects in the IPS have led to the suggestion that it is the locus of such a representation (Dehaene, 2003). In the current study we found distance effects in RT for both negative and positive numbers. Negative number comparisons also displayed a distance effect in accuracy, with near trials being significantly less accurate than far trials. Given these behavioral effects, we expected greater activity for near than far trials. Instead, whole brain univariate analyses did not show a significant effect of distance in the IPS, nor did we find a significant interaction between number type and distance. Cyto-architectonically defined ROIs showed a marginal effect of distance in the left IPS for negative problems, driven by strong activity for negative near trials. Taken together, these findings suggest that despite strong behavioral distance effects for positive and negative numbers, voxel-wise neural distance effects can be weak. Intermixing negative, positive, and mixed problems within each run may have increased transient responses from switching between problem types, which also drives IPS activity (Pessoa et al., 2009), making it difficult to detect the more subtle differences between near and far trials.

WEAK REPRESENTATION OF NEGATIVE NUMBERS IN IPS

In contrast to univariate analysis, RSA revealed differences between neural representations of near and far comparisons across the two number types. Neural responses in the IPS were less differentiated for negative than positive numbers. Specifically, there was greater similarity between the multi-voxel activity patterns for near and far negative number pairs than near and far positive pairs. That is, there were smaller neural representational distance effects for negative numbers than for positive numbers. Critically, increased representational differentiation between near and far negative numbers was associated with faster response times across subjects, consistent with a broader claim that greater differentiation in neural representation facilitates comparative processes. We suggest that greater experience with positive numbers leads to more distinct representations compared to negative numbers (Rosenberg-Lee et al., 2009). This view of a protracted refinement of IPS activity with experience is consistent with developmental research showing that children activate the IPS less than adults, but the differences are greater for symbolic number comparisons (Ansari et al., 2005) than for non-symbolic comparison (Ansari and Dhital, 2006).

Representational similarity analysis in both the functional and structural ROI implicated a mid-anterior region of the IPS, the hIP1, as a common locus of less differentiated representations for negative numbers. Resting state fMRI and diffusion tensor imaging analyses have shown that relative to the posterior-most IPS region hIP3, hIP1 has greater functional and structural connectivity with lateral prefrontal cortex, while hIP3 is more strongly connected to ventral visual areas (Uddin et al., 2010). Uddin et al. (2010) propose that hIP3 may transform incoming sensory information into quantity representations, whereas hIP1 "may support more complex aspects of numerical and mathematical information processing via their interconnections with fronto-parietal circuits" (Uddin et al., 2010, p. 2644). In light of these functional dissociations, the greater visual similarity between negative stimuli (i.e., the minus sign), might have suggested hIP3 as a likely area for RSA differences. Instead, the differences were in hIP1, suggesting that the representational difference between negative and positive numbers may reflect more abstract mathematical concepts.

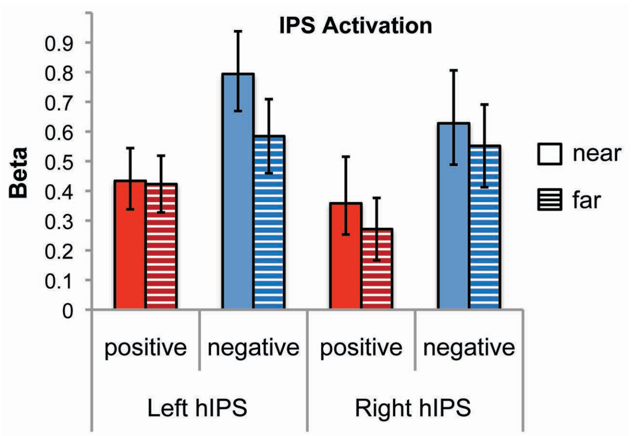

FIGURE 6 | Distance effects in cyto-architectonic maps of the intraparietal sulcus (IPS). There was significant activation for both number types and both distances in the left and the right IPS (combining hIP1, hIP2, and hIP3). There was a significant number type by distance by hemisphere interaction ($p = 0.028$). The left IPS showed a marginally significant effect of distance for negative numbers ($p = 0.059$) but not for positive numbers. Neither number type showed a distance effect in the right IPS.

PFC DIFFERENCES AND TASK DIFFICULTY

In contrast to the IPS, the prefrontal cortex was robustly engaged only for the more demanding task of negative number comparison. The left and right MFG also showed greater activation for negative, compared to positive, numbers. However, we did not find greater prefrontal cortex activation over baseline for positive numbers. While lateral prefrontal cortex activity is often reported for arithmetic tasks, previous studies of number processing have not consistently found activation in this area (Arsalidou and Taylor, 2011). Additional analyses using RT as a covariate in an ANCOVA model suggested that prefrontal activation could be related to task difficulty. More targeted experimental designs are needed to directly investigate this possibility.

CONNECTING fMRI RESULTS TO BEHAVIORAL RESEARCH ON NEGATIVE NUMBERS

Consistent with previous findings on integer comparison, we found that negative and positive number comparisons showed parallel distance effect slopes, but negatives took longer than positives. While prior behavioral studies have not reported accuracy differences (Tzelgov et al., 2009; Varma and Schwartz, 2011), the current study found that negative near problems were less accurate than positive near problems.

Based on extant behavioral literature, two theoretical models have been proposed for negative number processing. The *rule-based* processing model proposes that individuals reason about negative integers by applying abstract rules on top of magnitude representations for positive numbers (Fischer and Rottman, 2005; Shaki and Petrusic, 2005; Tzelgov et al., 2009). For example, when judging which of two negative integers is greater (−9 vs. −1), they may strip the negative signs and invert the comparison

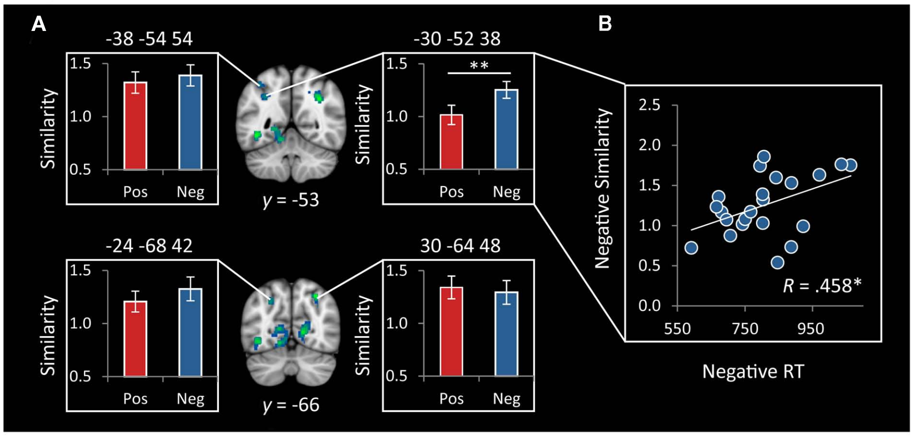

FIGURE 7 | Representational similarity in functionally defined IPS ROIs. **(A)** Representational similarity between near and far trials was greater for negative, compared to positive, numbers in the left IPS, centered at (−30, −52, 38; $^{**}p = 0.004$). There were no differences in the three other functionally defined IPS ROIs. **(B)** Representational similarity in the functional cluster centered at (−30, −52, 38) was correlated with reaction time (RT) on negative numbers ($^{*}p = 0.032$), such that more distinct representations were associated with faster reaction times. ROIs were 10mm spheres generated around peaks of differential IPS response to negative vs. positive numbers.

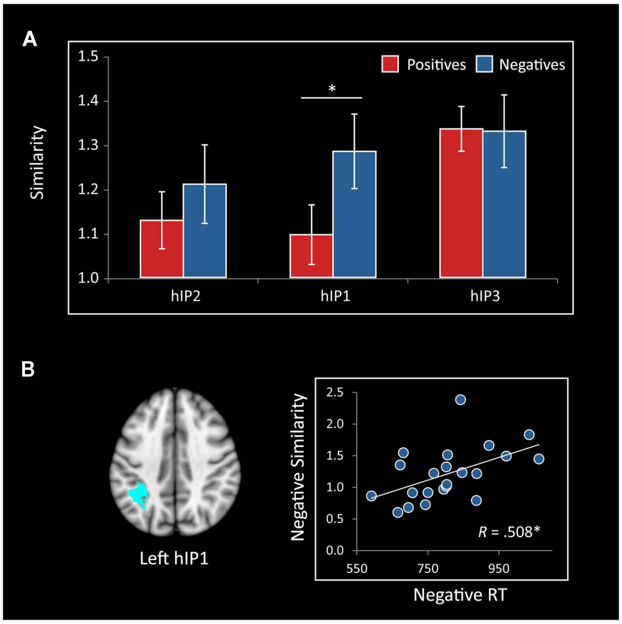

FIGURE 8 | Representational similarity in cyto-architectonically defined subdivisions of the IPS. (A) Representational similarity between near and far trials was greater for negative numbers than positive numbers bilaterally in hIP1 ($^*p = 0.027$). Differences in hIP2 and hIP3 were not statistically significant ($ps > 0.2$). **(B)** Representational similarity in the left hIP1 between near and far trials was correlated with reaction time (RT) on negative numbers ($^*p = 0.016$), such that more distinct representations were associated with faster reaction times.

predicate (greater → lesser), and subsequently rely on a positive mental number line to compare the absolute magnitudes (9 vs. 1). In this model, negative magnitudes are not represented uniquely, but are transformed into positive numbers for magnitude comparison.

The *expanded magnitude* model proposes that negative numbers (and zero) also have magnitude representations (Fischer, 2003; Varma and Schwartz, 2011). In this case, negative number representations play a direct role in magnitude comparison, as opposed to being translated into positive numbers. This implies that negative number magnitudes should have a separate neural representation distinct from positive numbers. Because adults have less experience with negative numbers than positive numbers, the neural representation of negative numbers may be less-refined than that of positive numbers. Furthermore, according to Varma and Schwartz (2011) the representation of negative magnitudes is organized as a reflection of the positives to instantiate the additional structure of the additive inverse ($X + -X = 0$).

The signal level differences found by univariate analyses in our study are consistent with either a *rule-based* or an *expanded magnitude* representation of negative numbers. Bilateral MFG activation could reflect rule processing, such as stripping the negative sign and inverting the comparison, or it could reflect general task difficulty. Conversely, greater bilateral IPS activation for negative numbers could reflect more effortful processing for negative over positive numbers, due to a less robust representation for negative numbers. Or, it could result from longer RTs and therefore longer time spent processing number. The signal level differences between negative and positive numbers help identify regions associated with negative and positive number representation, but do not differentiate the two models of number representation. This is because greater activation may be due to unspecified task difficulty. Consistent with this interpretation, controlling for RT removed the differences between negative and positive numbers in both frontal and parietal regions.

Representational similarity analysis provides a way to examine patterns of activation independent of overall signal level. RSA in both functionally and cyto-architectonically defined ROIs showed that in sub-regions of the IPS, representations of near and far positive numbers were more differentiated than near and far negative numbers. If the differentiation of far and near in negatives is functionally important, then we should predict an effect on behavior. This is what we found – a greater degree of differentiation among negative numbers was correlated with faster RTs. These findings point to a unique, but less well-developed, magnitude representation for negative numbers.

Alternate explanations are possible. For example, the application of rules might produce more noise in the positive magnitude representations when used for negative trials, resulting in decreased differentiation. However, if this were the case, prefrontal cortex activation for the application of a constant rule for negatives should not have diminished when covarying out RT (although caution should be taken when interpreting null results).

Our preferred interpretation, based on the RSA, is that an *expanded magnitude* hypothesis provides a parsimonious model of negative number representations for the current task. Future research manipulating instruction, such as by specifically asking participants to apply a rule-based strategy, could provide stronger causal evidence for this claim.

CONCLUSION

The field of cognitive neuroscience has focused considerable attention on how the natural numbers are represented in adults. During formal education, students are exposed to increasingly abstract quantitative relations, and mastery of these concepts forms a foundation for higher mathematics such as algebra and calculus. Yet little is known about how the brain enables and organizes abstract quantitative concepts. Examining negative numbers provides a first step toward a fuller understanding of the neural basis of these processes. The multivariate analysis technique used here reveals for the first time that negative numbers appear less well differentiated than positive numbers in the IPS, and that greater differentiation within negative number problems is associated with faster RT on negative problems. These findings support the proposal that people develop facility with negative numbers by creating a new representation that incorporates magnitude properties while remaining distinct from the natural numbers. Beyond the domain of negative numbers, our findings may reflect a general property of neural representation: that experience leads to greater differentiation between stimuli, even for abstract concepts.

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APPENDIX

WHOLE BRAIN RESULTS FOR MIXED COMPARISONS

As shown in **Table A1**, there were few differences between mixed and positive trials. The caudate, right precentral gyrus, and right cerebellum were more active for positive over mixed trials, and there were no significant clusters that were more active for mixed over positive trials. There were also no clusters that were more active for mixed over negative trials, though several regions that were more active for negative over mixed trials. These included bilateral cerebellum, bilateral intraparietal sulcus (IPS), bilateral superior parietal lobe (SPL), bilateral middle frontal gyrus (MFG), bilateral pre-supplementary motor area (SMA), the left precentral gyrus, left premotor cortex, left caudate, and the right frontal operculum cortex. Several regions more active for negative trials than mixed trials also showed greater activity in the contrast of negatives over positives, including bilateral MFG, bilateral IPS, and bilateral pre-SMA.

Table A1 | Activation differences between mixed comparisons and positive and negative comparisons.

Brain region	Peak				
	x	*y*	*z*	*t*	*k*
MIXED COMPARISONS > POSITIVE COMPARISONS					
No significant clusters					
POSITIVE COMPARISONS > MIXED COMPARISONS					
Bilat caudate	−6	6	8	4.86	133
Right precentral gyrus	46	4	40	4.44	33
Right cerebellum	34	−62	−28	4.43	63
MIXED COMPARISONS > NEGATIVE COMPARISONS					
No significant clusters					
NEGATIVE COMPARISONS > MIXED COMPARISONS					
Right cerebellum	30	−64	−28	7.37	1127
Left cerebellum	−24	−70	−20	6.97	874
Left IPS	−22	−60	46	6.21	1145
Left precentral gyrus	−54	0	42	5.77	306
Left MFG	−32	12	28	5.58	390
Right MFG	58	24	28	5.39	536
Bilat cerebellum	−6	−80	−22	4.35	306
Bilat pre-SMA	0	12	58	5.27	382
Right frontal operculum cortex	48	18	−4	5.08	85
Left premotor cortex	−26	−4	70	5	106
Right IPS	34	−58	42	4.98	302
Right MFG	36	6	64	4.94	67
Left SPL	2	−82	38	4.62	81
Left caudate	−14	16	−10	4.46	30
Left precentral gyrus	−54	8	20	4.28	62
Right SPL	32	−42	48	4.07	42

Table A2 | Parietal cortex regions that showed significantly greater activation for negative than positive problems and their relationship to cyto-architectonic maps of the parietal cortex.

Region	Number of voxels in the region	% of cluster in region	% of region activated
RIGHT IPS (30, −64, 48)			
R hIP1	48	11.9	21.1
R hIP3	45	11.2	14.8
R area 2	24	5.8	2.5
LEFT IPS (−30, −52, 38)			
L hIP1	22	25.0	4.8
LEFT IPS/SPL (−38, −54, 54)			
L hIP1	22	48.9	4.7
L hIP3	14	32.4	5.1
L SPL 7PC	3	7.4	1.6
L hIP2	2	4.5	0.9
L SPL 7A	2	4.5	0.1
L area 2	1	2.3	0.1
LEFT POSTERIOR IPS (−24, −68, 42)			
No overlap with cyto-architectonic areas			

For each significant cluster, the probabilistic region, percentage of activation in the region, percentage of cluster that was in the region is reported. Cyto-architectonically defined probability maps were used to interpret the locations of the cluster and peaks within subdivisions of the intraparietal sulcus (IPS), superior parietal lobule (SPL), and somatosensory Brodmann area 2.

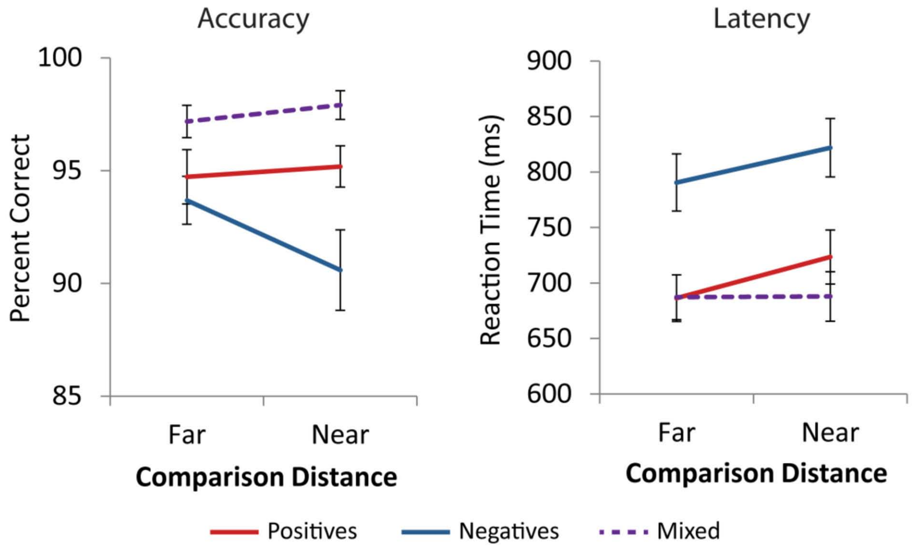

FIGURE A1 | Behavioral performance. Participants were significantly faster and more accurate on mixed comparisons than positive and negative comparisons ($p < 0.001$). Mixed comparisons did not display distance effects in accuracy ($p = 0.304$) or reaction time ($p = 0.890$). Error bars represent ±1 SE.

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Brain correlates of mathematical competence in processing mathematical representations

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The ability to extract numerical information from different representation formats (e.g., equations, tables, or diagrams) is a key component of mathematical competence but little is known about its neural correlate. Previous studies comparing mathematically less and more competent adults have focused on mental arithmetic and reported differences in left angular gyrus (AG) activity which were interpreted to reflect differential reliance on arithmetic fact retrieval during problem solving. The aim of the present functional magnetic resonance imaging study was to investigate the brain correlates of mathematical competence in a task requiring the processing of typical mathematical representations. Twenty-eight adults of lower and higher mathematical competence worked on a representation matching task in which they had to evaluate whether the numerical information of a symbolic equation matches that of a bar chart. Two task conditions without and one condition with arithmetic demands were administered. Both competence groups performed equally well in the non-arithmetic conditions and only differed in accuracy in the condition requiring calculation. Activation contrasts between the groups revealed consistently stronger left AG activation in the more competent individuals across all three task conditions. The finding of competence-related activation differences independently of arithmetic demands suggests that more and less competent individuals differ in a cognitive process other than arithmetic fact retrieval. Specifically, it is argued that the stronger left AG activity in the more competent adults may reflect their higher proficiency in processing mathematical symbols. Moreover, the study demonstrates competence-related parietal activation differences that were not accompanied by differential experimental performance.

Keywords: angular gyrus, mathematical competence, fMRI, arithmetic, fact retrieval, symbol–referent mapping

INTRODUCTION

Mathematical competence is one of the key cognitive abilities that is acquired through formal schooling. In general, it is a central component of human intelligence and thus highly relevant for educational and occupational attainment (Neisser et al., 1996; Schmidt and Hunter, 1998). In particular, it is essential for making informed decisions in various areas of life as most of the information on which decisions are based is numerical (Parsons and Bynner, 2005). This holds particularly true in health decisions: Low mathematical competence (or low numeracy) was found to be associated with inadequate perception of risks and benefits of screening, reduced medication compliance, and, eventually, poor medical outcomes (Reyna et al., 2009). This impairment in decision-making may not only be traced back to deficits in numerical magnitude processing but also to a lack of understanding different mathematical representations such as tables, graphs, or symbolic equations (Lipkus and Peters, 2009).

In light of the considerable progress in understanding the brain mechanisms underlying number processing (for a review, cf. Ansari, 2008), there is still little research into the brain correlates of individual differences in mathematical skills. Much of this research has focused on learning disabilities in mathematics (developmental dyscalculia) and has revealed abnormal brain function and structure in the parietal cortex, specifically in the intraparietal sulcus (IPS; cf. Rubinsten and Henik, 2009; Butterworth et al., 2011). Using functional magnetic resonance imaging (fMRI), Price et al. (2007) found that distance between numbers in a simple number comparison task (requiring to decide which of two numbers is larger) less strongly modulated right IPS activation in dyscalculic compared to control children. Likewise, dyscalculic children were reported to show weaker IPS activation in approximate calculation than controls (Kucian et al., 2006). These results are complemented by voxel-based morphometry (VBM) studies revealing less gray matter density and volume in the IPS of dyscalculics compared to controls (Isaacs et al., 2001; Rotzer et al., 2008). At present, there is wide consensus that the IPS holds an amodal and format-independent representation of numerical magnitude and is therefore systematically engaged in any task drawing on magnitude manipulations – from basic number comparison to complex calculation (Dehaene et al., 2003, 2004). This suggests that one basis of learning disabilities in mathematics lies in impaired numerical magnitude processing, which is also in line with the findings from behavioral research (e.g., Butterworth and Laurillard, 2010).

Even though the IPS, as the core quantity system, can be assumed to play the most important role in many number processing demands, studies on adults' mathematical competence within the normal achievement range suggest that more and less competent individuals do not differ in the engagement of this brain region during calculation. Rather, they seem to differentially activate the left angular gyrus (AG; Menon et al., 2000; Grabner et al., 2007, 2009a,b). Grabner et al. (2007) screened a large sample of adults with respect to their cognitive abilities and then contrasted the brain activation patterns between two groups of mathematical competence (which did not differ in verbal or figural–spatial abilities) while they were performing easy and more difficult multiplication problems. The data revealed that the more competent individuals displayed higher activation of the left AG during multiplication and that the left AG activation level was linearly related to individuals' score in the mathematical competence test. The less competent participants did not activate any brain region more strongly (for similar evidence, see Grabner et al., 2009a).

The left AG is another brain area whose activation is frequently modulated during number processing, especially during mental calculation (Ansari, 2008; Zamarian et al., 2009), but its functional role is less well understood than that of the IPS. In their influential review paper on parietal circuits in number processing, Dehaene et al. (2003) proposed that the left AG belongs to the language system and may support the retrieval of verbally stored arithmetic facts from memory (such as the multiplication table). This notion has been corroborated by studies showing higher left AG activation while solving multiplication compared to subtraction problems (Lee, 2000), in applying fact retrieval compared to procedural (calculation) strategies (Grabner et al., 2009a), and in trained compared to untrained arithmetic problems (Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007). Against this background, Grabner et al. (2007) interpreted the finding of higher left AG activation in the more competent individuals to reflect a stronger reliance on arithmetic fact retrieval. In other words, participants with higher mathematical competence could have solved the multiplication problems more frequently by fact retrieval than their less competent peers. This interpretation was corroborated in a training study in which the individuals of both competence groups were trained on a set of multiplication problems before they were presented with trained and untrained problems in the fMRI test session (Grabner et al., 2009b). It was shown that mathematical competence had an impact on performance and left AG activation only in the untrained but no longer in the trained problems. Precisely, the more competent individuals displayed stronger left AG activation and better performance in the novel problems, but in the trained problems, when both competence groups could retrieve the multiplication facts from memory, the activation and performance difference diminished.

The retrieval of arithmetic facts from memory, however, may only be one function of the left AG in mathematical problem solving that differs between more and less competent individuals. There is growing evidence that activation of this brain region is also modulated in numerical tasks that do not draw on mental calculation or arithmetic fact retrieval. Holloway et al. (2010) administered a symbolic (Arabic digits) and non-symbolic (arrays of squares) number comparison task in which participants only had to indicate the side with the larger quantity. Consistent with several previous studies on magnitude processing (cf. Dehaene et al., 2003) both task conditions (contrasted with control tasks) activated the IPS. But most interestingly, the contrast between the task conditions revealed larger left AG activation in the symbolic (compared to the non-symbolic) representation. This result was replicated by Gullick et al. (in press) applying a similar experimental design. Moreover, Price and Ansari (2011) have reported that even passive viewing of Arabic digits compared to unfamiliar symbols and letters is associated with stronger activation of the left AG. These findings suggest that the left AG subserves a more fundamental cognitive function in mathematical thinking than just arithmetic fact retrieval. One promising candidate for this function is symbol processing. Numerous studies have implicated the AG in the processing of linguistic symbols, in particular in the mapping of graphemes to phonemes or in the mapping of words (as symbolic chunks) to their semantic referents (for reviews, cf. Price, 2000; Price, 2010). Against this background, Ansari (2008) proposed that this brain region supports similar cognitive processes in the mathematical domain. According to his symbol–referent mapping hypothesis, the AG subserves the automatic mapping between mathematical symbols and their semantic referents. In basic number processing, it is assumed that the presentation of a numerical symbol (e.g., an Arabic digit) automatically activates the internal semantic representation (e.g., the magnitude representation). This hypothesis is also compatible with neuroimaging studies on mental arithmetic as over-learned arithmetic problems (e.g., the multiplication table or extensively trained problems) could have become higher-order symbols (symbolic chunks, similar to words) whose presentation automatically activates the associated solution in memory.

It is important to note that the functional interpretation of the left AG in mathematical cognition is often hindered by the observation of deactivations compared to baseline conditions. In fact, the majority of findings in mathematical information processing reflect modulations of relative deactivation rather than activation (e.g., Zago et al., 2001; Ischebeck et al., 2006; Venkatraman et al., 2006). This partly holds true for its relation with mathematical competence. For instance, Grabner et al. (2007, 2009b) reported strong relative deactivations during mental arithmetic in the less competent adults, whereas their more competent peers exhibited a weak deactivation or some activation compared to a resting-state baseline.

Taken together, studies on mental arithmetic have revealed that adults of lower and higher mathematical competence differ in the activation of the left AG. However, it is unclear whether this activation difference indeed reflects differential reliance on arithmetic processes or whether it is related to a more general function in mathematical cognition. In the present fMRI study, we sought to answer this question by administering a task drawing on another key component of mathematical competence besides mental arithmetic, i.e., the processing of multiple mathematical representations (NCTM, 2000). Concretely, we presented adults of lower and higher mathematical competence (again matched in verbal and figural–spatial abilities) with a representation matching task, requiring them to indicate whether the mathematical information in a symbolic equation and a bar chart is identical or not. In order to evaluate the role of mental arithmetic in the link between mathematical competence and AG activity, two task conditions without and one condition with arithmetic demands were administered. If the previously observed competence-related activation differences in the left AG during mental arithmetic were indeed due to differential reliance on arithmetic processes (in particular, arithmetic fact retrieval), the individuals of lower and higher mathematical competence should only exhibit left AG activation differences in the task condition with arithmetic demands. If, however, these competence-related activation differences were due to a more general process in mathematical cognition, such as symbol processing, the groups should differ in left AG activation also in the task conditions without arithmetic demands.

Another aim of the present study was to further specify the anatomical localization of potential competence-related activation differences in the parietal cortex by additionally using probabilistic cytoarchitectonic maps (Eickhoff et al., 2005; Caspers et al., 2006). This is of particular importance for a better understanding of the AG in mathematical thinking. First, the activation clusters assigned to the AG in previous fMRI studies on number processing exhibit a high anatomical heterogeneity (see, for instance, the review paper by Dehaene et al., 2003). Second, the findings in the mathematical domain can often hardly be integrated with those in other domains as various (topographically less exact) labels for this brain region have been used (e.g., temporo-parietal junction, inferior parietal cortex). And, third, cytoarchitectonic studies of post-mortem brains have shown that the parietal cortex has a more fine-grained anatomical structure than is reflected in standard atlases used in fMRI studies (Caspers et al., 2008; Zilles and Amunts, 2010). The applied probabilistic cytoarchitectonic maps divide the AG into an anterior (PGa) and a posterior (PGp) part and the supramarginal gyrus into five areas (PFop, PFt, PF, PFm, and PFcm).

MATERIALS AND METHODS

PARTICIPANTS

Prior to the fMRI study, a pool of 179 adults (66 males) was screened with respect to their mathematical competence (by means of a mathematics test; Ibrahimovic and Bulheller, 2005) and their intelligence structure (Berlin Intelligence Structure Test; BIS-T; Jäger et al., 1997). From this pool, we selected two groups of participants for the fMRI test session (with 18 adults each; half males) who only differed in their mathematical competence but not in verbal and figural–spatial abilities (by using a similar procedure as described in Grabner et al., 2007, 2009b). The data of six participants had to be excluded from the analysis due to technical problems (one participant) or excessive movement (larger than 3 mm in translational or 3° in rotational direction) during fMRI data acquisition (five participants). The descriptive data of the remaining sample of 28 participants (15 males) is presented in **Table 1**. Two-sample t-tests revealed that the group of higher mathematical competence (higher math group; $n = 14$) displayed significantly higher scores in the mathematics test, $t(26) = -8.08$, $p < 0.001$ than the group of lower mathematical competence (lower math group, $n = 14$). However, both groups did not differ significantly in verbal intelligence, $t(26) = 0.64$, $p = 0.53$, figural–spatial intelligence, $t(26) = -1.03$, $p = 0.31$, nor in age, $t(26) = -0.73$, $p = 0.47$. All participants were healthy, right-handed, and had normal or corrected-to-normal vision. They gave written informed consent and were paid for their participation. The study was approved by the local ethics committee (Medical University of Graz, Austria).

Table 1 | Descriptive statistics of age and psychometric test data of the lower ($n = 14$) and higher ($n = 14$) mathematical competence group.

	Lower math competence		Higher math competence	
	M	**SD**	***M***	**SD**
Age (years)	22.36	3.10	23.07	1.98
Mathematical competence	94.43	7.81	116.82	6.82
Verbal intelligence	102.14	5.98	100.77	5.35
Figural–spatial intelligence	98.01	8.68	100.75	4.86

Test scores are given in IQ scale (M = 100, SD = 15).
Mathematical competence was assessed by means of the scale "arithmetic and algebra" of the mathematics test (Ibrahimovic and Bulheller, 2005); verbal and figural–spatial intelligence by means of the Berlin Intelligence Structure Test (BIS-T; Jäger et al., 1997).

EXPERIMENTAL TASKS AND PROCEDURE

In the fMRI test session, participants worked on a mathematical representation matching (REP) task. In each problem, they were presented with a bar chart (with three variables: a, b, c) plus a symbolic equation, and had to evaluate whether the mathematical information in both representation formats is identical or not (see **Figure 1**). Three experimental conditions were administered. In the easiest condition (REP1), the equation described the magnitude of one variable (e.g., "$a = 14$"), in the second condition (REP2), the minimum or maximum magnitude of the three variables was given (e.g., "max = 13"), and in the most complex condition (REP3) an additional calculation (addition or subtraction of numbers between 1 and 6) was included (e.g., "min + 2 = 18"). Each condition comprised 42 problems. The numerical magnitude of the target variable (i.e., the variable named in REP1 or the correct value in REP2 and REP3) was between 1 and 10 (small numbers) for half of the problems and between 11 and 20 (large numbers) for the other half of the problems. Even and odd numbers were equally distributed across problems within each condition. In REP2 and REP3 minimum values were small numbers and maximum values were large numbers. In REP3 the calculation required addition or subtraction of numbers between 1 and 6. The magnitude of the distractor variables (i.e., the two other variables besides the target variable) in each problem were calculated by adding or subtracting numbers between 1 and 3 (for one distractor variable) or between 4 and 6 (for the other distractor variable). In each condition, half of the equations correctly matched the bar chart, whereas in the other half of the equations the value of one distractor bar was given.

The 126 problems (42 per condition) were presented in an event-related fMRI design consisting of 3 runs with 42 problems

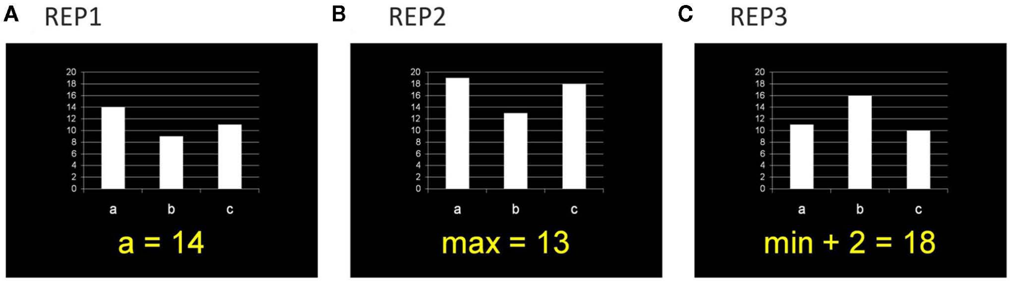

FIGURE 1 | Example items for the three task conditions in the representation matching task (REP). Participants had to evaluate whether the mathematical information in the symbolic equation and the bar chart is identical or not. **(A)** In REP1, the equation described the magnitude of one variable. **(B)** In REP2, the minimum or maximum of the three variables was given. **(C)** In REP3, an additional calculation was included.

each (14 problems per condition). The order of the problems was pseudo-randomized. Each problem was presented for 4 s, followed by an inter-trial interval of 3–5 s (jittered in 1 s steps across the problems, $M = 4$ s) during which a fixation point was presented on the screen. Participants responded by pressing the right-hand button if the mathematical information in the equation was identical to that of the bar chart and the left-hand button if it was not. Each run started with the number of the run (1–3) presented on the screen for 3 s, followed by a 25-s fixation period. At the end of each run, another fixation period of 20 s was included. Before imaging was performed, participants were familiarized with task and response mode and solved 12 practice problems (4 problems per REP condition). Instructions stressed speed and accuracy. The total experimental time was about 20 min.

DATA ACQUISITION AND ANALYSIS

Imaging was performed on a 3.0 T Tim Trio system (Siemens Medical Systems, Erlangen, Germany) using an 8-channel head coil. To minimize head movement, subjects' heads were stabilized with foam cushions. Functional images were obtained with a single shot gradient echo EPI sequence sensitive to blood oxygen level-dependent (BOLD) contrast (TR = 2000 ms, TE = 30 ms, FA = 90°, matrix size = 64 × 64, spatial resolution = 3 mm × 3 mm). In total, 586 functional volumes (first two were discarded to allow for signal stabilization) with 31 transverse slices (3 mm thickness, 0.09 mm gap) were acquired in descending order. Structural images were obtained using a T1-weighted 3D MPRAGE sequence (TR = 1900 ms, TE = 2.22 ms) which provided 1 mm isotropic resolution. Stimulus presentation was accomplished with the Eloquence system (Invivo Corporation, Orlando, FL, USA), containing an LCD display with full XGA solution, visible for the participant through a mirror mounted above the head coil. The paradigm was presented using the software package Presentation (Neurobehavioral Systems, Albany, CA, USA). For responding, two response boxes were placed in the participants' left and right hand, respectively. Responses were given with the index finger of the right or left hand.

Functional magnetic resonance imaging data analysis was performed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). The functional data of each participant were motion-corrected, slice-time corrected, spatially normalized into the standard Montreal Neurological Institute (MNI) space (based on the EPI template using the original voxel size of 3 mm × 3 mm × 3 mm), and smoothed using a Gaussian kernel of 8 mm FWHM. The statistical analysis was conducted on the basis of the general linear model as implemented in SPM. Model time courses for correctly solved problems in each experimental condition (REP1, REP2, REP3) and incorrectly solved problems were generated on the basis of the hemodynamic response function as given by SPM5. The time interval during the presentation of the run number (for 3 s, at the beginning of each run) and the six motion parameters were entered into the model as regressors of no interest. A high-pass filter with a cut-off frequency of 1/256 Hz was employed to remove low frequency drifts. In the analysis, the activation pattern related to each experimental condition was first computed by linear t-contrasts for each participant individually. In a second step, these images were entered into a random-effect analysis in which the two groups of mathematical competence were contrasted by means of a two-sample t-test for independent samples. Significant activation differences between the groups in each condition were identified using an initial voxel-wise threshold of $p < 0.001$ uncorrected. Only activation clusters significant at $p < 0.05$ FWE corrected for multiple comparisons at cluster level are reported. To evaluate whether the observed activation differences reflect differences in relative activation or deactivation, respectively, we extracted the individual beta weights from region-of-interests (ROIs). The anatomical location of the significant activation clusters was analyzed by means of the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and probabilistic cytoarchitectonic maps (Caspers et al., 2006, 2008) as implemented in the SPM Anatomy toolbox (Eickhoff et al., 2005).

Behavioral data (accuracy and response latencies of the correctly solved problems) were analyzed using repeated measures ANOVAs with task condition (REP1, REP2, REP3) as within-subject factor and math competence group (lower vs. higher) as between-subject factor. In all analyses, degrees of freedom were corrected for violations of the sphericity assumption by means of the Huynh–Feldt procedure; the probability of a Type I error was maintained at 0.05. If applicable, uncorrected df values together with the corrected p value and the Huynh–Feldt epsilon (ε) are reported.

RESULTS

BEHAVIORAL DATA

The ANOVA on the accuracy data revealed a main effect of task condition, $F(2{,}52) = 50.55$, $p < 0.001$, $\eta^2 = 0.66$, $\varepsilon = 0.81$, as well as an interaction of task condition and math competence group, $F(2{,}52) = 4.31$, $p < 0.05$, $\eta^2 = 0.14$. As depicted in **Figure 2A**, the accuracy was very high (above 95%) in the conditions REP1 and REP2, whereas it was remarkably lower in REP3. *Post hoc t*-tests revealed significant differences between all three conditions, all ts$(27) > 2.40$, ps < 0.05. Importantly, only in REP3 a significant performance difference between the mathematical competence groups emerged: The more competent individuals solved the problems more accurately than their less competent peers, $t(26) = -2.29$, $p < 0.05$.

In the response latencies, in contrast, no effect of mathematical competence but only a significant main effect of task condition was found, $F(2{,}52) = 579.62$, $p < 0.001$, $\eta^2 = 0.96$, $\varepsilon = 0.86$. As expected, the longest response latencies were observed in REP3, followed by REP2 and REP1 (see **Figure 2B**). All differences between task conditions reached significance in *post hoc* comparisons, ts$(27) > 5.10$, $p < 0.001$.

fMRI DATA

Contrasting the brain activation of the two competence groups only revealed significantly higher activation in the mathematically more (compared to less) competent individuals. Most interestingly, however, the anatomical location of the activation differences was strikingly similar for all three task conditions: It mainly covered the left AG but also included parts of the supramarginal gyrus and the inferior parietal cortex (see **Table 2** and **Figure 3**). No other brain regions displayed significant activation differences between groups. The beta weights of the three clusters showed that the observed activation difference is due to strong relative deactivation in the individuals of lower mathematical competence and weak relative activation in the more competent peers.

The probabilistic cytoarchitectonic localization of the competence-related activation difference is presented in **Table 3** and depicted in **Figure 4A**. In all three task conditions, the largest part of the activation clusters lay within the left anterior AG (area PGa), followed by areas of the supramarginal gyrus (PFm, PF, and PFcm). To further evaluate whether the activation in the left anterior AG also differed between the task conditions and whether this may interact with the math competence group, we additionally extracted the individual beta weights from the anatomically defined PGa region in the left hemisphere. An ANOVA with task condition and math competence group only yielded a large main effect of math competence group, $F(1{,}26) = 24.86$, $p < 0.001$, $\eta^2 = 0.49$. As depicted in **Figure 4B**, the activation levels of both groups in the left PGa did not differ as a function of task condition and display a stronger deactivation in the group of lower compared to higher mathematical competence.

DISCUSSION

In the present fMRI study, we investigated the brain correlates of mathematical competence in a task drawing on the core ability to process mathematical representations (NCTM, 2000; Reyna et al., 2009). Specifically, we were interested in the functional significance of activation differences in the left AG observed in previous studies on mental arithmetic (Menon et al., 2000; Grabner et al., 2007, 2009b). To this end, we presented adults of lower and higher mathematical competence with a representation matching task that either only involved the processing of two representations (symbolic equation and bar chart) or additionally required mental arithmetic.

The behavioral data revealed that both groups of mathematical competence performed equally well in the two task conditions without arithmetic demands. This was true in terms of accuracy as well as response latencies. Mathematical competence only had an impact on accuracy when participants had to additionally perform a simple mental calculation (addition or subtraction). In the fMRI data, however, significant effects of mathematical competence were observed in all three task conditions: The individuals of higher mathematical competence displayed stronger activation of the left AG extending to the supramarginal gyrus than their less

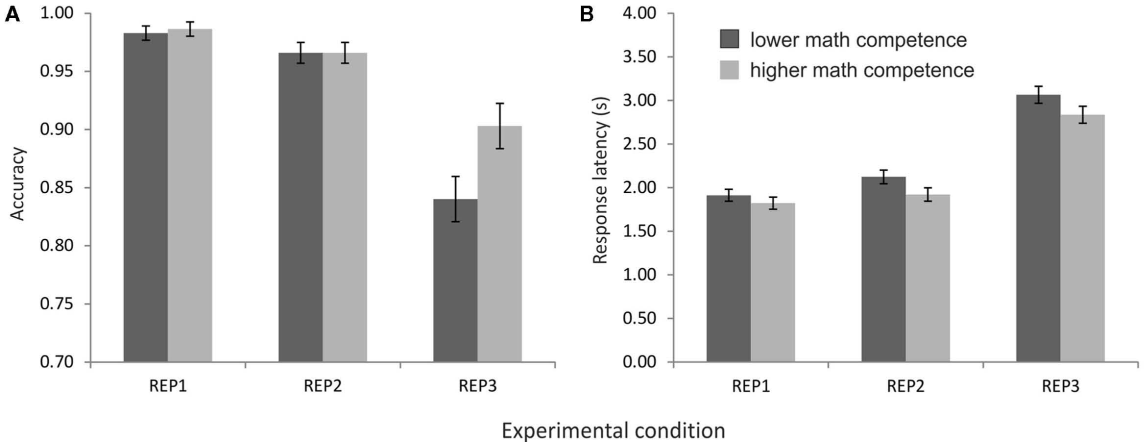

FIGURE 2 | Performance of the mathematical competence groups in the representation matching task (REP), presented separately for the three task conditions. (A) Accuracies. **(B)** Response latencies of the correctly solved problems.

Table 2 | Overview of activation clusters emerging in the contrasts of higher > lower mathematical competence in the three experimental conditions of the representation matching task (REP).

Condition	Region	Cluster (%)	*x*	*y*	*z*	*k*	*t*
REP1	L AG	63.64	−48	−54	27	55	5.30
	L SMG	23.64					
	L IPC	12.73					
REP2	L AG	54.43	−48	−51	27	79	5.43
	L SMG	25.32					
	L IPC	20.25					
REP3	L AG	31.34	−48	−60	48	67	4.64
	L IPC	49.25					
	L SMG	17.91					

Coordinates refer to the activation peak of the cluster and are reported in Montreal Neurological Institute (MNI) space as given by SPM5. The anatomical localization is presented based on the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The first label denotes the location of the peak activation, further labels indicate different brain regions within the same activation cluster (including submaximal). The percentage of activated voxels within the respective brain regions is also presented.

Only activation clusters significant at $p < 0.05$ FWE corrected for multiple comparisons at cluster level are reported.

L, left hemisphere; AG, angular gyrus; SMG, supramarginal gyrus; IPC, inferior parietal cortex.

competent peers. The present findings extend previous research on the brain correlates of adults' mathematical competence in two ways.

First, they demonstrate that adults of lower and higher mathematical competence show different brain activation patterns in mathematical thinking which are not accompanied by performance differences in the experimental task. In all previous studies, competence-related activation differences were confounded with differential task performance levels (Menon et al., 2000; Grabner et al., 2007, 2009b). This considerably compromised the functional interpretation of AG activation in relation to mathematical competence as it could not be ruled out that the activation differences can be attributed to differences in relative task difficulty. The AG is part of the default-mode network (DMN; Raichle et al., 2001) which typically displays lower relative activity (larger deactivation) in more difficult task conditions (McKiernan et al., 2003; Buckner et al., 2008). Since such an association between task difficulty and AG activation has been reported in practically all fMRI studies on mental arithmetic (for reviews, cf. Dehaene et al., 2003; Zamarian et al., 2009), some authors argued that the engagement of the left AG is related to difficulty-related modulations of the DMN rather than to task-specific cognitive processes (e.g., Zago et al., 2001; Wu et al., 2009). Consequently, a lower relative activity (larger deactivation) in the less (compared to the more) competent individuals may merely reflect a stronger (negative) modulation of the DMN because the task is more difficult for these individuals (in terms of accuracy and/or response latencies). The present finding of competence-related left AG activation differences in the absence of experimental performance differences stands in contrast to this explanation. Notably, a recent study on mental arithmetic has added further evidence against the difficulty explanation of AG activity in mathematical cognition. Grabner et al. (in press) investigated the neural correlates of the well-established associative confusion effect (Winkelman and Schmidt, 1974) that consists of poorer performance while verifying addition and multiplication equations whose solutions are associated with the other operation (confusion equations; e.g., "$9 \times 6 = 15$") compared to solutions unrelated to both operations (non-confusion equations; e.g., "$9 \times 6 = 52$"). In comparing both task conditions, it was found that the more difficult confusion equations were associated with higher relative activation in the left AG, which is also opposite to the typical behavior of the DMN.

Second, the present study revealed that adults of higher mathematical competence more strongly activated the left AG while processing mathematical representations independently of whether the task requires cognitive processes related to mental arithmetic. The left AG activation (in the PGa region) neither differed between the task conditions nor was the competence effect moderated by them. This finding sheds new light onto the functional significance of competence-related activation differences in the left AG. In particular, it precludes the account that processes related to mental arithmetic underlie competence-related activation differences in the left AG. If this had been the case, then a different result pattern should have emerged in the condition in which an additional mental calculation had to be carried out. This also holds true for the fact retrieval account since only calculations of small problem size (results smaller or equal 20 with addends and subtrahends between 1 and 6) were presented, which are likely to be solved by retrieving the solution from memory (Campbell and Xue, 2001; Grabner and De Smedt, 2011).

Thus, the obtained findings indicate that the left AG supports a more general cognitive function in which adults of lower and higher mathematical competence differ. Besides the aforementioned fact retrieval and task difficulty accounts, it has been proposed that this brain region is implicated in the processing of mathematical symbols such as Arabic digits or even equations (Ansari, 2008; Holloway et al., 2010; Price and Ansari, 2011; Grabner et al., in press). The current results can be reconciled with this view as in all three conditions of the representation matching task participants were required to process the symbolic equation (e.g., "$a = 14$") and to compare this information with the graphical representation. Following this contention, the differential left AG activation in the two competence groups may reflect subtle differences in the proficiency of mathematical symbol processing which did not appear in behavior.

At present, the most prominent account on the function of the AG in mathematical symbol processing is the symbol–referent mapping hypothesis (Ansari, 2008). According to this hypothesis, the AG supports the automatic mapping of mathematical symbols onto semantic representations, similar to the function of the AG in linguistic symbol processing. At the basic level, this mapping could occur between Arabic digits and the internal magnitude representation (similar to grapheme–phoneme mappings) but also mappings between symbolic chunks (e.g., arithmetic equations) and higher-order semantic knowledge (e.g., arithmetic solutions) have been discussed (similar to the associations between words and their meaning). While the present results are inconsistent with

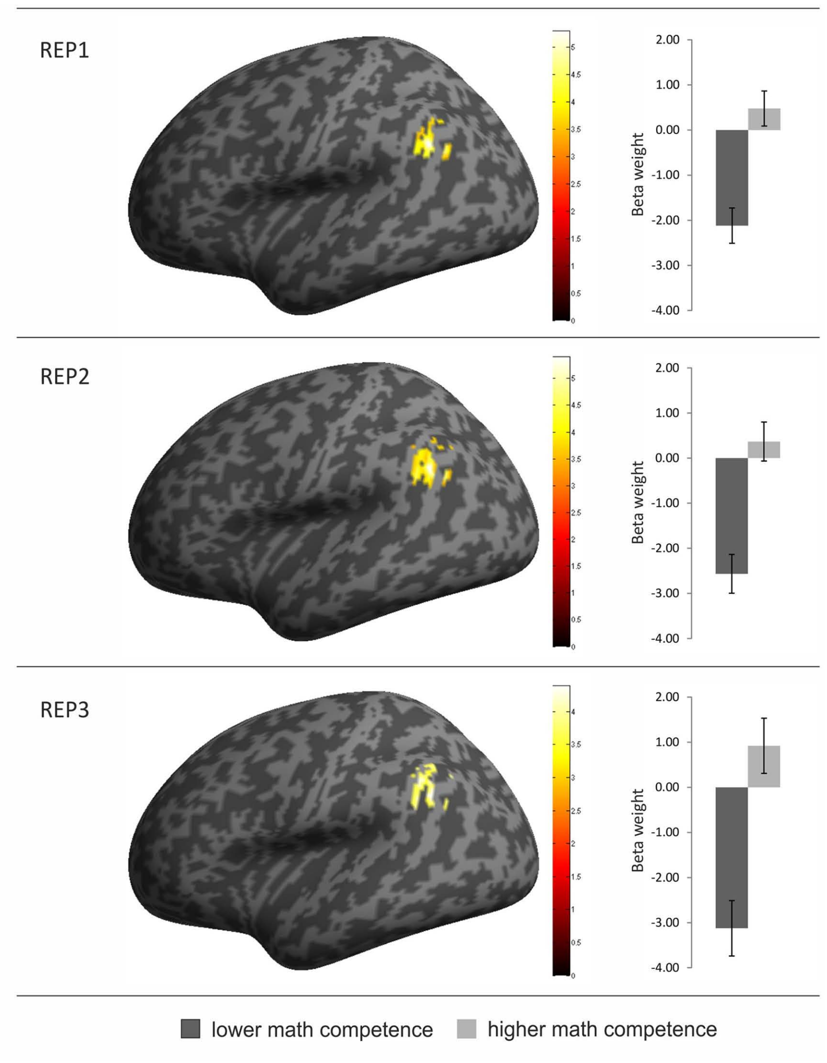

FIGURE 3 | Overview of brain regions with greater activation in the individuals of higher (compared to lower) mathematical competence in the three conditions of the representation matching task (REP). The activation clusters are depicted on an inflated brain in left lateral view (left part of the figure). In addition, the beta weights from the three activation clusters are presented separately for the two math competence groups. Error bars depict ± 1 SE of the mean.

competence-related differences in mappings between arithmetic equations and solutions, the data do not allow to draw conclusions regarding which type of symbols are differentially processed in mathematically more and less competent individuals. It may be speculated that the groups already differ in the proficiency of processing number symbols. This assumption would be in line with recent evidence showing that the automatic access of magnitude information from symbolic representations is key in the development of mathematical competence (e.g., Rousselle and Noel, 2007; Iuculano et al., 2008; Holloway and Ansari, 2009; De Smedt and Gilmore, 2011).

Two current models on the general functional significance of the (anterior) AG are largely consistent with the symbol–referent mapping hypothesis. First, the ventral parietal cortex comprising the AG and the supramarginal gyrus have been linked to bottom-up attentional processes during direct memory retrieval. Specifically, in their attention-to-memory (AtoM) model, Cabeza et al. (2008) argued that the automatic activation of memory contents upon the presentation of an external cue (such as in automatic symbol–referent mapping) is due to bottom-up attentional processes which are mediated by the ventral parietal cortex. Top-down attentional processes engaged in retrieval after controlled memory search, in contrast, have been linked to areas of the dorsal (superior) parietal lobe (centered on the IPS). This view has been corroborated by findings of higher inferior parietal activation for items that were recognized with high compared to low confidence (Chua et al., 2006), for strong compared to weak memories (Shannon and Buckner, 2004), and for memory retrieval facilitated by semantic priming (Whitney et al., 2009). Second, there is increasing consensus that the left AG supports semantic

Table 3 | Probabilistic cytoarchitectonic localization of left-hemispheric activation clusters emerging in the contrasts of higher > lower mathematical competence in the three experimental conditions of the representation matching task (REP).

Condition	Region	Activated region (%)	Cluster (%)	Peak prob. (%)	*x*	*y*	*z*
REP1	PFm	4.80	13.20	30/50	−48	−54	27
	PGa	8.80	39.40	30/60			
	PF	1.60	8.10	n.a./20			
REP2	PGa	13.10	40.60	40/30	−48	−51	27
	PFm	11.90	22.60	20/40			
	PF	1.60	6.00	20/n.a.			
REP3	PGa	13.90	50.90	70/30/40	−48	−60	48
	PFm	16.20	36.10	50/20/60			
	PF	1.30	5.50	n.a./40/40			
	PFcm	2.90	5.00	n.a./n.a./10			

Coordinates refer to the activation peak of the cluster and are reported in Montreal Neurological Institute (MNI) space as given by SPM5. The anatomical localization is presented based on the probabilistic cytoarchitectonic maps from the SPM Anatomy toolbox (Eickhoff et al., 2005). The first label denotes the (probabilistic) location of the peak activation, further labels indicate different brain regions within the same activation cluster (including submaxima) if the percentage of activated voxels within the cluster is ≥ 5.00. In addition, percentage of activation within the region, percentage of cluster within the region, and peak probabilities for all significant activation maxima (first probability refers to peak activation) are shown.

Only activation clusters significant at $p < 0.05$ FWE corrected for multiple comparisons at cluster level are reported.

information processing, in particular semantic integration and knowledge retrieval (Binder et al., 2009; Price, 2010). Seghier et al. (2010) additionally presented evidence that the dorsal AG (corresponding to area PGa) may specifically support the search for a semantic representation, which is a process that is likely engaged during symbol–referent mapping.

A central limitation of applying these models to the domain of mathematics, however, lies in the frequent observation of relative deactivations in the left AG even in task conditions that should elicit bottom-up attention processes or semantic information processing (Cabeza et al., 2008; Binder et al., 2009). In the present study, we observed strong relative deactivation in the less competent individuals, whereas their more competent peers displayed some activation above resting-state baseline (see **Figure 3**). This finding is consistent with Grabner et al. (2007) who reported an association between mathematical competence and peak activation in the left AG that ranged from deactivation to activation. The functional significance of this (de-)activation pattern is still an unresolved issue, and studies with multiple baseline conditions other than fixation are needed. Direct memory retrieval (e.g., Mazoyer et al., 2001) and semantic processes (e.g., Binder et al., 1999) have been proposed to spontaneously occur during resting state so that any task-related activation increase or decrease may reflect higher and lower engagement of these processes compared to baseline. In reference to the symbol–referent mapping hypothesis, Holloway et al. (2010) recently suggested that this deactivation may reflect a filter mechanism that is engaged whenever symbols cannot be mapped onto their semantic referents in order to allow for alternative processing. However, since no brain regions turned out to be more active in the less competent individuals, it remains elusive what alternative processing may take place if this filter is engaged.

Even though the symbol–referent mapping hypothesis provides a rational framework in which the present and many other findings have been discussed, it is important to point out that its prediction regarding the mapping of numerical symbols onto magnitude representation lacks direct empirical support from training studies so far. Lyons and Ansari (2009) required young adults to associate novel geometrical symbols with approximate numerical magnitudes during fMRI and did not find modulations of AG activity in a number comparison task involving the novel symbols. In contrast, the left IPS and prefrontal brain regions responded to magnitude processing. Similar evidence was reported by Diester and Nieder (2007) who trained two monkeys to assign visual shapes to numerical magnitudes in a delayed match-to-sample task. They recorded the neural activity from single cells in the prefrontal cortex and the IPS (but not in the AG) and observed that the responses of many prefrontal neurons were modulated by the numerical value. These findings demonstrate important roles of prefrontal and IPS regions in the early learning of associations between numerical symbols and magnitudes but do not rule out the assumption that the AG may be involved in the automatic semantic processing of numerical symbols after extended practice or in a later stage of development (Grabner, 2009). Several fMRI studies have revealed that the activation of the AG and the IPS underlie considerable developmental activation shifts (for a review, cf. Ansari, 2010). Moreover, significant activation increases in the AG have been reported after a 5-day training of the association between numerical facts and three-dimensional geometric objects (Grabner et al., 2009b). Therefore, future studies need to address the potential interplay of the prefrontal cortex, the IPS, and the AG in symbol–referent mapping.

The application of probabilistic cytoarchitectonic maps has revealed that the activation difference between the mathematical competence groups was mainly located in area PGa of the AG which corresponds to the results of all previous studies on number processing reporting probabilistic cytoarchitectonic regions (Wu et al., 2009; Rosenberg-Lee et al., 2011; Grabner

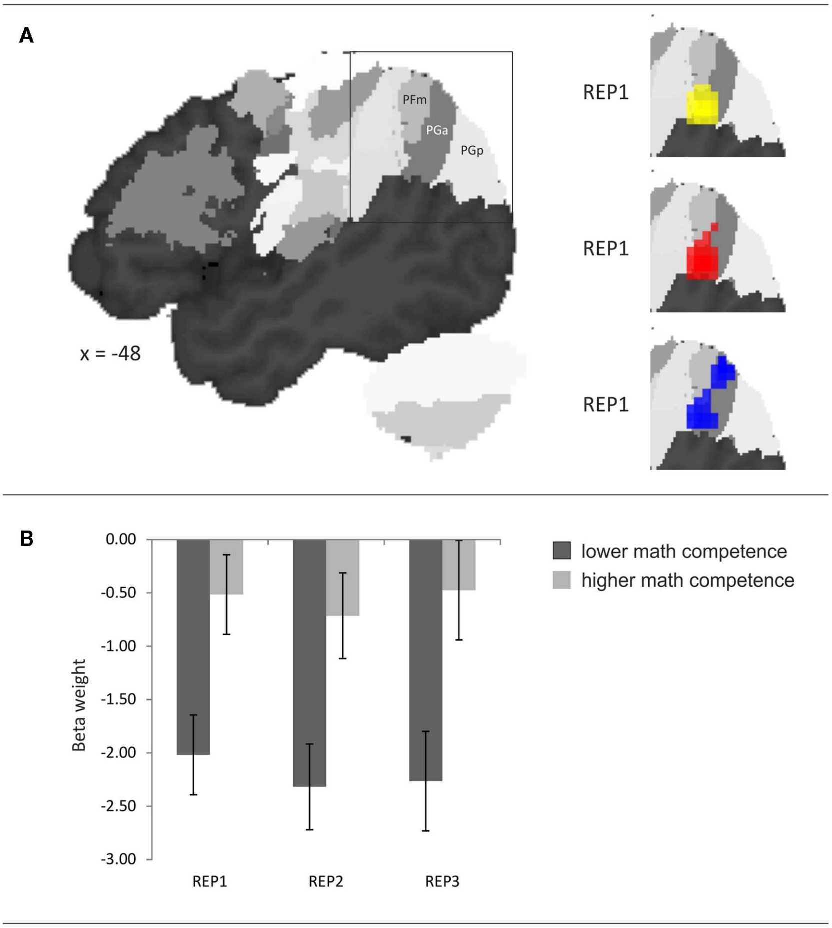

FIGURE 4 | (A) Probabilistic cytoarchitectonic localization of the left-hemispheric activation cluster emerging in the contrast higher > lower mathematical competence in the three conditions of the representation matching task (REP). **(B)** Effect of mathematical competence on beta weights in area PGa. Error bars depict ± 1 SE of the mean.

et al., in press). Wu et al. (2009) found stronger PGa (and PGp) activation in mental arithmetic using Arabic compared to Roman digits. Notably, this result also nicely fits into the symbol–referent mapping hypothesis as Arabic digits are highly overlearned and can be expected to be more automatically mapped onto the semantic magnitude representation than Roman digits. Rosenberg-Lee et al. (2011) reported associations between performance in multiplication and division problems and the left PGa. Finally, also the aforementioned associative confusion effect in the Grabner et al. (in press) study was accompanied by activation increases in the area PGa. These and the present findings demonstrate a functional differentiation between the anterior and posterior AG (areas PGa and PGp) and provide first evidence that area PGa may be primarily associated with mathematical information processing, in general, and symbol processing, in particular.

In conclusion, the present study has revealed that mathematically more (compared to less) competent adults display stronger left (anterior) AG activity in a task drawing on the ability of processing multiple mathematical representations. The activation difference between competence groups was not moderated by the presence or absence of arithmetic demands, which indicates that it cannot be attributed to a differential reliance on arithmetic processes such as fact retrieval. Rather, the present results add to current evidence suggesting an important role of the left AG in the processing of symbolic mathematical representations. The stronger activity in the more competent adults may thus reflect a higher proficiency in this cognitive function. Moreover, this study provides the first demonstration of differential parietal activation patterns in mathematically more and less competent adults that were not accompanied by performance differences in the experimental task.

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