Left parietal TMS disturbs priming between symbolic and non-symbolic number representations

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ABSTRACT

An amodal number representation activated by all types of numerical input, irrespective of the input notation, has often been proposed to be located in the left or right intraparietal sulcus (IPS). Two cross-notational priming experiments were carried out to test the existence of a notation-independent magnitude representation in the left or right parietal lobes. In Experiment 1, stimuli were Arabic digits and number words. Results revealed no significant effect of repetitive transcranial magnetic stimulation (rTMS) over left or right IPS during prime presentation. In contrast, in Experiment 2, digits and dot patterns were intermixed and here the priming distance effect (PDE) was reduced in the right TMS condition and absent for stimulation over left IPS. These findings suggest: (1) that TMS over left but not right IPS disrupts processes that are crucial for priming when symbolic and non-symbolic stimuli are intermixed, and (2) that disruption of the left IPS on its own is not sufficient to disrupt cross-notational priming when purely symbolic number notations are used. Our results point towards a crucial role of the left hemisphere for the mapping between small symbolic and non-symbolic numerosities.

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1. Introduction

Humans share with animals an ability to process magnitudes, often referred to as the approximate number sense (Cantlon, Platt, & Brannon, 2009a; Agrillo, Piffer, Bisazza, & Butterworth, 2012). When children grow older and are confronted with symbols to represent numbers, these symbols acquire meaning by being associated with this non-symbolic system (Mundy & Gilmore, 2009). However, it is still debated how these systems are represented in the human brain and how links between the culturally acquired symbol and the non-symbolic system are established over the course of development: some suggest there is a single, notation-independent representation that codes numerical quantity for all types of numerical input (e.g. digits, verbal numbers, dot patterns) (e.g. Dehaene, Dehaene-Lambertz, & Cohen, 1998; McCloskey, 1992; Piazza, Pinel, LeBihan, & Dehaene, 2007). Others have argued in favor of notation-dependent representations that are associated to one another (Cohen Kadosh & Walsh, 2009).

Behaviorally, magnitude representation is commonly investigated with the priming paradigm (e.g. Koechlin, Naccache, Block, & Dehaene, 1999; Reynvoet, Brysbaert, & Fias, 2002): Two numbers are presented sequentially and the size of the first number (prime) influences the response to the second number (target). This typically leads to a priming distance effect (PDE), i.e. targets preceded by numerically close primes (e.g. "1" preceded by "2") are responded to faster than targets preceded by primes that are numerically further away (e.g. "1" preceded by "4"). Traditionally, this PDE is explained by assuming a magnitude representation on a mental number line (Dehaene, 1997): Magnitudes are represented on a left-to-right oriented line as a distribution around the true location of each specific number, with partially overlapping representations with nearby numbers. This implies that, whenever a magnitude is presented, not only the representation of that specific magnitude will be activated, but also partially the representation of nearby numbers. To test the idea of a notation-independent magnitude representation, priming experiments have been set up with primes and targets in different notations. For instance, Reynvoet et al. (2002) showed that the priming distance effect was unaffected by notation changes between prime and target and therefore suggest a notation-independent magnitude representation (see also Herrera & Macizo, 2008; Naccache & Dehaene, 2001). Cohen Kadosh (2008) however, found a larger priming distance effect for digits than for number words, suggesting that digits and number words are processed by a notation-dependent code.

The issue of a notation-independent magnitude representation has also been addressed in imaging studies. fMRI studies have investigated whether similar activations are found for different

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numerical input. For instance, Holloway and Ansari (2010) presented participants with a symbolic and non-symbolic comparison task and corresponding control tasks. They found increased activation in the right inferior parietal lobe near the intraparietal sulcus (IPS) for both notations (see also Pinel, Dehaene, Riviere, & LeBihan, 2001). Similarly, Libertus, Woldorff and Brannon (2007) demonstrated that the event-related potentials (ERPs) during a symbolic and non-symbolic comparison task had similar time courses for the different notations and Dehaene (1996) observed in his ERP study a similar voltage pattern for Arabic digits and verbal numerals, suggesting a notation-independent magnitude representation. However, the observation of similar patterns of activations for different notations does not necessarily imply a single notation-independent magnitude representation (Cohen Kadosh, Bahrami, Walsh, Butterworth, Popescu, & Price, 2011). Therefore, recently, several imaging studies were conducted using the fMRI adaptation paradigm. fMRI adaptation is a technique that is based on the observation that the fMRI signal is reduced when the same stimulus is presented repeatedly (Grill-Spector & Malach, 2001). For example, Naccache and Dehaene (2001) presented number primes and targets as digits (e.g. 1) or as number words (e.g. one) and observed response suppression in both the left and the right parietal cortex when the same quantity was presented, irrespective of notation change (see also Notebaert, Pesenti, & Reynvoet, 2010). Piazza et al. (2007) investigated the extent to which similar populations of neurons responded to symbolic (i.e. Arabic digits) and non-symbolic (i.e. dot arrays) stimuli. Subjects were first adapted to dot patterns or digits and then a new number was presented in either the same or a different notation. Piazza et al. (2007) observed a numerical adaptation effect in the left and right intraparietal sulcus (IPS) and frontal regions irrespective of notation change. In the left parietal lobe however, there was also an abnormal recovery from adaptation when deviant dots were presented among Arabic digits. Together, these studies support the idea of a notation-independent (i.e. with different symbolic formats or a combination of symbolic and non-symbolic formats) magnitude representation in both parietal cortices.

However, not all studies with this technique found evidence for notation-independent coding in the left and right IPS. For example, Cohen Kadosh, Cohen Kadosh, Kaas, Henik and Goebel (2007) observed a left/right parietal asymmetry: they found magnitude adaptation, irrespective of notation change, in the left IPS. In the right IPS, however, they failed to find any evidence for a notation-independent magnitude representation. More recently, Cohen et al. (2011) observed, by means of an effective connectivity analysis between left and right IPS, that the effect of magnitude change was affected by a change in numerical format (e.g. from digits to dot patterns). Based on these results, the authors concluded that not only the right IPS (e.g. Cohen Kadosh et al., 2007), but also the left IPS houses notation-dependent magnitude representations.

From both behavioral and imaging studies, it is clear that it remains open, first, whether magnitude representations in the left and the right IPS are notation-dependent or notation-independent and second, if the IPS activation in priming tasks is causally related to the behavioural PDE. To help clarifying these issues, we disrupted processing in the left and right IPS with repetitive transcranial magnetic stimulation (rTMS) during cross-notational priming. Our aim was to investigate whether there is a causal relationship between the activity in left and right IPS and the notation-independent priming effect (Walsh & Cowey, 2000). More specifically, adults conducted a purely symbolic (i.e. digits and number words, Experiment 1) and a mixed non-symbolic symbolic (i.e. digits and dot patterns, Experiment 2) priming task, and were stimulated with rTMS over the left and the right IPS. Additionally, there was a control condition in which sham TMS

was applied over the a control region. TMS pulses were delivered during the prime presentation to disrupt the semantic processing of the prime and the effect of the prime on target processing that typically results in the priming distance effect. If the left and right IPS do indeed house a notation-independent representation for magnitude, the priming distance effect should be disrupted by rTMS.

2. Experiment 1

2.1. Participants

Seventeen healthy participants ($M_{age}=22$ years, $SD=4.2$ years, 10 males) recruited from an academic environment, took part in the study, after giving their informed consent. They received £10. All participants were right-handed, had no history of neurological or psychiatric disorders, had normal or corrected-to-normal vision, and were unaware of the purpose of the study. All of them were screened for TMS exclusion criteria and were negative for the risk factors associated with TMS (Keel, Smith, & Wasserman, 2002). The procedures were performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration; the experimental protocol received ethical approval from the Research Governance Committee at York Neuroimaging Center (YNIC), University of York.

2.2. Apparatus, procedure and stimuli

In a lit room, subjects were seated at a distance of approximately 50 cm from the computer screen and wore bathing caps. On these caps, the relevant coordinates for stimulation were marked (see Section 2.2.1). For generating the magnetic pulses, a Magstim stimulator, Model Super Rapid (The Magstim Co. Ltd., Whitland, UK) with a 70 mm figure of eight coil was used. The intensity of the magnetic stimulation was set separately for each individual depending on their motor threshold (at 110% active motor threshold). Motor threshold was defined as minimum percentage of the stimulator output that evoked a visually detectable twitch in the contralateral hand when contracted. Frequency, intensity and duration of the repetitive transcranial magnetic stimulation (rTMS) were in accordance with the safety guidelines suggested by Wassermann (1998). The experimental task was conducted using a 15-inch color screen connected to a computer running the Windows XP operating system. Stimulus presentation and the recording of behavioral data (reaction time and accuracy) were controlled by E-prime 1.1 (Psychology Software Tools, http://www.pstnet.com).

Participants were asked to decide as fast as possible but without making errors whether a stimulus was smaller or larger than five, by pressing the left or right button on the keyboard ('q' or 'p' on an QWERTY keyboard). All participants used the same response assignment, because of its consistency with the association between space and magnitude (i.e. the SNARC-effect; Dehaene, Bossini, & Giraux, 1993). Primes and targets appeared in the center of the screen until a response was detected. Stimuli (Arial font, 20) for both primes and targets were numbers 1, 4, 6 and 9, presented as either Arabic digits (for example, 1 or 4) or as written verbal number words (for example, ONE or FOUR). The interstimulus interval was 200 ms (see Fig. 1 for the timeline of a trial). The numerical distance between two subsequent stimuli in each trial was always 0 or 3. All possible combinations of distances zero and three were presented resulting in 16 congruent trials, (i.e. trials in which the response to target and prime was identical, e.g. 1–FOUR) combined with eight incongruent trials (i.e. trials in which the first stimulus or the 'prime' was smaller than five and
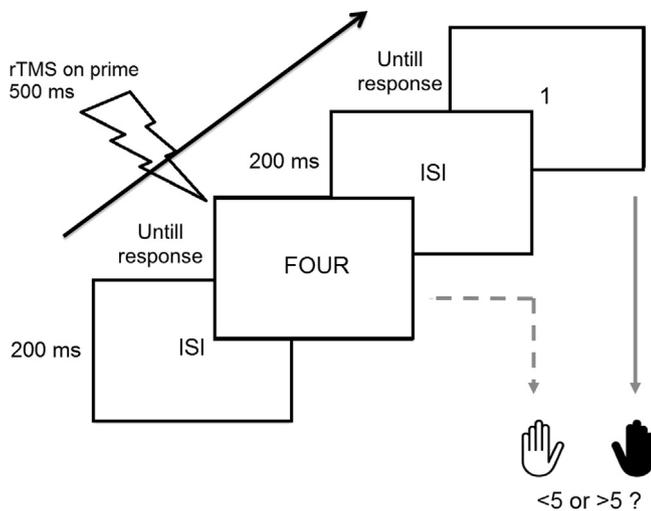
Fig. 1. Example of a trial. Both prime and target remained on the screen until a response was detected. Prime and target were Arabic digits (e.g. 1 or 4) or number words (e.g. ONE or FOUR).
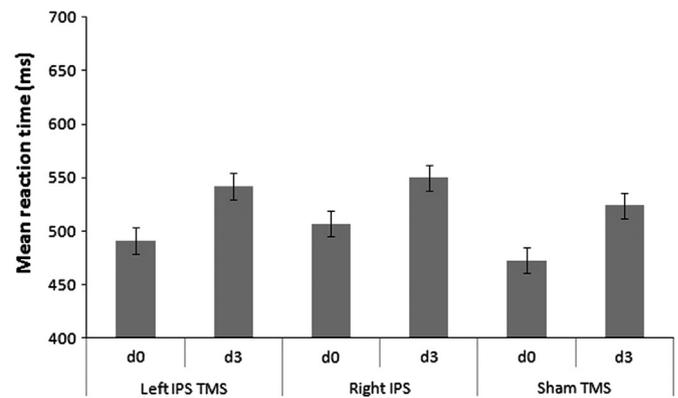

Fig. 2. Experiment 1: Reaction times and standard errors in ms to targets with prime-target numerical distance of 0 or 3 for symbolic stimuli (Arabic digits and number words).

the second stimulus or the 'target' was larger than five, e.g. 1–SIX). Only responses to congruent trials were included in the data analysis. Each unique combination was presented once with rTMS and seven times without rTMS, resulting in 192 trials in total that were presented pseudo randomly. In the TMS trials, rTMS was applied over the subject's scalp for 500 ms at 10 Hz starting with the onset of prime presentation. As is standard for TMS studies using a new paradigm, we chose to use repetitive TMS, because we were not sure about the exact time window in which the prime is processed. Each participant completed the experimental task with the 192 trials three times: with rTMS over the left IPS, over the right IPS and with sham TMS (i.e. with a fully functional coil but held in a 90 degree angle, horizontally from the left to the right hemisphere over the vertex). The order of stimulation to the left and the right IPS and sham stimulation was counterbalanced between participants.

2.2.1. Localization of stimulation sites

In an fMRI study of number priming (Notebaert, Nelis, & Reynvoet, 2011) activation in the left IPS ($x=-42$, $y=50$, $z=-46$) was found to increase linearly with the numerical distance between prime and target. We used the MNI-coordinates of the peak of this activation (Montreal Neurological Institute, http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) and its homologue in the right IPS ($x=42$, $y=50$, $z=46$) as our targets sites for left and right IPS stimulation. These IPS coordinates do not diverge significantly from the sites reported in previous fMRI studies (e.g. Cohen Kadosh et al., 2011, 2007; Piazza et al., 2007). Scalp positions for optimal stimulation of those target sites were localized in each participant by the following procedure: first a Polaris infra-red tracking device (Northern Digital, Ontario, Canada) was used to measure the position of the subject's head, then Brainsight software (Rogue Research, Montreal, Canada) was used to co-register the subject's head with the subject's MRI scan (T1-weighted anatomical scans from a GE 3 T HDx Excite MRI system) and to identify the exact scalp position to target the left and right IPS sites.

2.3. Results

Mean accuracies were 91% ($SD=9\%$), 91% ($SD=8\%$) and 91% ($SD=8\%$) for the left IPS, the right IPS and the sham condition respectively. A repeated measures Analysis of Variance (ANOVA)

with site (three levels: left IPS, right IPS and sham) and distance (two levels: d_0 and d_3) as within subjects factors was conducted on the reaction times of the subjects' correct responses. A main effect of distance was observed ($F(1,16)=20.95$, $p < .001$, $\eta_p^2=.57$), demonstrating faster reaction times for the smallest distance (see Fig. 2), i.e. a significant PDE. There was no main effect of site ($F(2,15)=1.58$, $p=2.24$, $\eta_p^2=.17$) and no significant site by distance interaction ($F < 1$).

2.4. Discussion

In order to test the causal role of IPS activation for a notation-independent priming effect, we carried out a priming experiment in which participants were stimulated over the left and the right IPS during prime presentation. Additionally, sham TMS over the vertex was administered as a control condition. Behaviourally, results showed a cross-notational priming distance effect in all three conditions: participants responded faster to targets that were preceded by primes that were numerically identical to the target. TMS had no significant effect on RTs: the priming distance effect (PDE) was equally large after the left IPS, the right IPS and the sham TMS. This, in line with some previous imaging studies (e.g. Naccache & Dehaene, 2001; Notebaert et al., 2010), suggests that both hemispheres house a notation-independent representation. Consequently, interference in either the left IPS or the right IPS caused by TMS is not sufficient to disrupt the PDE overall, because the notation-independent magnitude representation in the opposite hemisphere can still evoke a PDE. Alternatively, the absence of a TMS effect could also be explained by the existence of a symbolic number representation located outside the IPS regions. However, the latter explanation is rather unlikely given the many fMRI studies that found only adaptation in the IPS for this type of stimuli (e.g. Notebaert et al., 2010; Piazza et al., 2007; Cohen Kadosh et al., 2007).

In this experiment, we used two symbolic notations for number. In a recent study, Lyons, Ansari and Beilock (2012) demonstrated that adults were significantly faster comparing two symbolic quantities (i.e. digits–digits or digits–number words) than comparing symbolic to non-symbolic quantities (i.e. digits–dots). The authors suggested that the additional processing cost for comparing symbolic to non-symbolic quantities can be explained by assuming distinct representational systems for symbolic and non-symbolic quantities. In order to examine the effect of the activation of symbolic and non-symbolic representations, we conducted a second experiment with a cross-notation priming task, using Arabic digits and dot patterns as stimuli.

3. Experiment 2

3.1. Participants, procedure and stimuli

The participants, the procedure and the experimental task were identical to Experiment 1, only the stimuli differed. Stimuli for both primes and targets were numbers 1, 4, 6 and 9, presented as either Arabic digits (for example, 1 or 4) or as dot patterns (for example four dots). Non-symbolic stimuli were white-filled circles (radius 3.5 cm) containing a set of black dots presented on a black background. Dot patterns were generated with a MatLab script (Dehaene, Izard, & Piazza, 2005) and dot size and total area were systematically varied.

3.2. Results

Mean accuracies were 89% (SD=9%), 87% (SD=12%) and 90% (SD=8%) for the left IPS, the right IPS and the sham condition, respectively. A repeated measures Analysis of Variance (ANOVA) with site (three levels: left IPS, right IPS and sham) and distance (two levels: d_0 and d_3) as within subjects factors was conducted on the reaction times of the subjects' correct responses. A main effect of distance was observed ($F(1,16)=8,76$, $p < .01$, $\eta_p^2=.35$), demonstrating faster reaction times for the smaller distance (see Fig. 3). There was no main effect of site ($F < 1$). Moreover, a marginal significant site by distance interaction was observed ($F(2,15)=3.04$, $p=.08$, $\eta_p^2=.29$). Pairwise comparisons showed a significant PDE in the sham condition ($p < .01$; one-sided). After stimulation over the right IPS, the effect was still marginally significant ($p=.07$, one-sided). However, no PDE was observed after left IPS stimulation ($p=.70$).

4. General discussion

In this study, we employed repetitive transcranial magnetic stimulation to investigate whether there are notation-independent representations in the IPS. In particular, we first asked whether there are hemispheric differences in the IPS contribution towards these representations and second, whether it matters if stimuli are symbolic, non-symbolic or mixed. Evidence in favour of a notation-independent representation is mixed: some studies have suggested that the left and the right IPS possess a notation-independent representation (Naccache & Dehaene, 2001; Notebaert et al., 2010), while other studies have argued in favour of a notation-independent representation in the left hemisphere only (Cohen Kadosh et al., 2007) and still other studies seem to suggest that magnitude representations are notation-dependent (Cohen Kadosh et al.,

Fig. 3. Experiment 2: Reaction times and standard errors in ms to targets with prime-target numerical distance of 0 or 3 for symbolic and non-symbolic stimuli (Arabic digits and dots).

2011). To clarify this issue, we stimulated over the left IPS or the right IPS during a cross-notational priming task in two experiments (i.e. digits–word numbers in Experiment 1; digits–dots in Experiment 2). Behavioural studies have demonstrated that the performance in such a task is typically described by a priming distance effect (PDE), i.e. faster RTs when the prime is close to the target, even when prime and target have different notations (Reynvoet et al., 2002). If either left or right IPS alone are responsible for this priming effect, the behavioural PDE should be disturbed after rTMS stimulation.

In Experiment 1 we found no evidence for a disturbance by rTMS, no differences were found between the sham TMS condition and the conditions in which the participants were stimulated with rTMS over the left and the right IPS, which is in line with a bilateral notation-independent representation (Naccache & Dehaene, 2001; Notebaert et al., 2010), i.e. the disruption of a number representation in one hemisphere is not sufficient to cause a disruption in the behavioural PDE because the representation in the other hemisphere is intact and sufficient for creating the PDE. In contrast, in Experiment 2, a significant effect of rTMS was found. A significant PDE was present in the sham condition, but a smaller PDE when participants were stimulated over the right IPS. The PDE disappeared completely when the participants were stimulated with rTMS over the left IPS. This indicates that the left IPS is crucial for the integration of non-symbolic and symbolic stimuli and suggests either a notation-independent representation in the left hemisphere or a crucial contribution of the left IPS towards non-symbolic magnitude representation that cannot be compensated for by the right IPS. How can the results of both experiments be reconciled?

The mainstream idea is that humans share with animals a non-symbolic system that enables us to process and compare numerosities (Cantlon et al., 2009a; Xu & Spelke, 2000). When children learn number words and Arabic digits, these symbols acquire meaning only through the connection with the non-symbolic magnitude representation (Dehaene, 1992; Mundy & Gilmore, 2009). However, several recent findings are not consistent with this idea. Behavioral studies showed that an individual's distance effects in symbolic and non-symbolic comparison, another behavioral indicator of the underlying magnitude representation next to priming, are not related (Holloway & Ansari, 2009; Maloney, Risko, Preston, Ansari, & Fugelsang, 2010; Sasanguie, De Smedt, Defever, & Reynvoet, 2012). Similarly, studies in children with developmental dyscalculia have demonstrated intact performance in non-symbolic comparison, whereas a significant impairment was present in symbolic number processing (De Smedt & Gilmore, 2011; Iuculano, Tang, Hall, & Butterworth, 2008; Landerl & Kölle, 2009; Rouselle & Noël, 2007). Both findings are difficult to reconcile with the idea that, once theses representations are established, symbols and non-symbolic stimuli still call upon the same fundamental magnitude representation. Lyons et al. (2012) recently proposed the idea that the culturally acquired symbolic system and the non-symbolic system are more weakly associated than previously has been assumed. According to these authors, over development, the non-symbolic system and the culturally acquired symbolic system gradually diverge from each other and when both symbolic and non-symbolic representations need to be activated, as for instance in a mixed-notation comparison task, an *additional processing cost* is the result. In their study, these authors indeed observed that adults had more difficulties with comparing symbolic and non-symbolic quantities than comparing two symbolic quantities.

The present data fit with this account. In Experiment 2, RTs—indexing processing time- were significantly longer than in Experiment 1, $t(16)=-3.00$, $p < .01$, $d=-0.73$. In Experiment 1, stimuli were number words and Arabic digits 1 to 9. These are
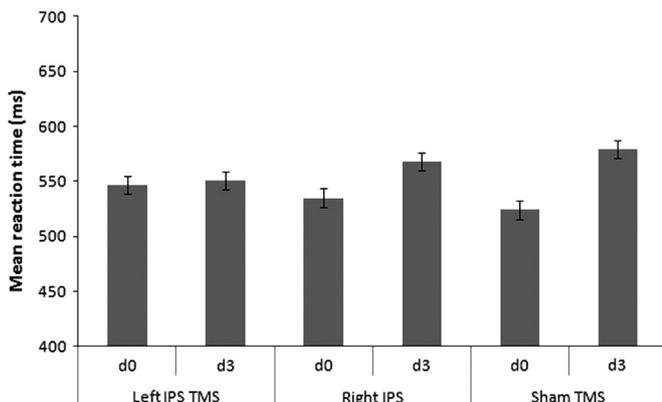
high frequency items that adults are highly familiar with. Furthermore, upon the presentation of those items adults access its exact semantic representation easily and automatically (e.g. Kaufmann et al., 2008; Fias, Reynvoet, & Brysbaert, 2001). In contrast, in Experiment 2, symbolic and non-symbolic stimuli were used. The physical features of the non-symbolic stimuli, i.e. the dot patterns were systematically varied (i.e. in terms of item size, total area and dot locations), to prevent the participants to use these features to solve the task. A direct automatic access from the dot patterns to the semantic representation thus was made impossible or at least more difficult. Thus in this second experiment, participants first had to extract the exact numerosity from the non-symbolic display before they could compare it to five. This additional step can be considered as the additional 'processing cost' in terms of Lyons et al. (2012).

It is possible that the right IPS is involved in moving spatial attention (e.g. Coull & Frith, 1998) while extracting numerosity from the non-symbolic displays. This could account for the marginal TMS effect for stimulation over the right IPS.

Stimulation over left IPS, however, led to a stronger and clear disruption of the priming distance effect when symbolic and non-symbolic stimuli were used. This suggests that the left IPS is contributing to the conversion of non-symbolic to symbolic representations. We suggest that the left IPS is crucial for this conversion because of its anatomical and functional connections. Evidence for this stems from neuroimaging studies documenting regions outside the parietal regions that exhibit significant activation to both Arabic numerals and dot array in adults (Cantlon et al., 2009b). There are several candidates outside the IPS that could be involved in the semantic mapping between symbolic and non-symbolic number representations. For example, IPS neurons are connected to the dorso-lateral prefrontal cortex, a region in which association neurons, i.e. neurons responding to both non-symbolic and symbolic quantity representations, have been found in monkeys (Diester & Nieder, 2007). These association neurons seem to rely on IPS input and play a crucial role in the semantic mapping process from non-symbolic to symbolic representations. Symbolic number representations might thus only be indirectly connected to non-symbolic number representations (Nieder, 2009). In human development language plays a part in establishing this connection and thus retrieval of semantic associations in adults is likely to be left-lateralised. Ansari (2008) suggests that the left parietal lobe is specialised in encultured magnitude representations resulting from connections with left fronto-parietal regions involved in language processing. Non-symbolic stimuli might thus be processed in both left and right IPS but only the left IPS might provide the connections to semantic mapping areas crucial for the non-symbolic to symbolic conversion.

In their numerical fMRI adaptation study, Piazza et al. (2007) also observed a hemispheric asymmetry: in the right IPS there was a distance-dependent effect in recovery from adaptation irrespective of notation change, whereas there was no such effect in the left IPS when deviant dots were presented among Arabic digits. Piazza et al. (2007) suggested that the observed asymmetry might be due to the fact that the right hemisphere is more involved in approximate judgements, while the left is more important for exact number processing (see also Andres, Seron, & Olivier, 2005). However, we do not believe that this explanation can account for our results. If the left hemisphere were more important for exact number processing, one would expect rTMS over the left IPS to disturb exact number processing and thus show an effect in Experiment 1 too. Following Piazza's et al. (2007) reasoning, a changed PDE would then be expected. Contrary to this expectation, magnetic stimulation over left IPS in Experiment 1, however, did not alter the PDE.

In short, we conducted two priming experiments while stimulating the left and the right IPS, in order to shed light on the debate of the existence of notation-independent magnitude representations. Our results indicate that disruption of the left or right IPS alone is not sufficient to disrupt the priming distance effect when symbolic stimuli are used. However, the priming distance effect between symbolic and non-symbolic numerosities is disrupted by left IPS TMS suggesting a crucial role of the left hemisphere for the mapping between small symbolic and non-symbolic numerosities. Possibly, the gradual diversion of the non-symbolic and symbolic representational system over development is the cause of this necessary mapping process (Lyons et al., 2012).

Acknowledgments

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